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TABLE OF CONTENTS FIRST PAGE

A SCIENTIFIC CORNER

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THE SOLUTIONS, AS SOLVED BY EXPERIENCE, INDICATED!

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"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"

CONTENTS

Original Articles

Toxoplasma Chorioretinitis in Adults PAGE

Helenor Campbell Wilder, Washington, D. C. 127

Cerebral Electric Response to Intermittent Photic Stimulation in Amblyopia ex Anopsia

Hermann M. Burian, M.D., Iowa City, and C. Wesley Watson, M.D., with the Technical Assistance of Marjorie M. Edmond, B.A., Boston 137

Comparison of Results of Cortisone Treatment by Instillation and by Subconjunctival Injection

I. C. Michaelson, F.R.F.P.S.(Glas.); D.O.M.S.; Ph.D.(Glas.), Haifa, Israel 144

Clinical Evaluation of the Aqueous-Flow Test

Andrew deRoetth Jr., M.D., and Willis S. Knighton, M.D., New York 148

Congenital Ectasia of the Cornea

Hugh C. Donahue, M.D., Boston 154

Registry of Interesting Cases

Extreme Axial Hyperopia

William F. Hatcher, M.D., Roanoke, Va. 161

Annual Reviews

Pharmacology and Toxicology

Irving H. Leopold, M.D., Philadelphia 163

Society Transactions

New York Academy of Medicine, Section of Ophthalmology 262

Regular Departments

News and Comment 270

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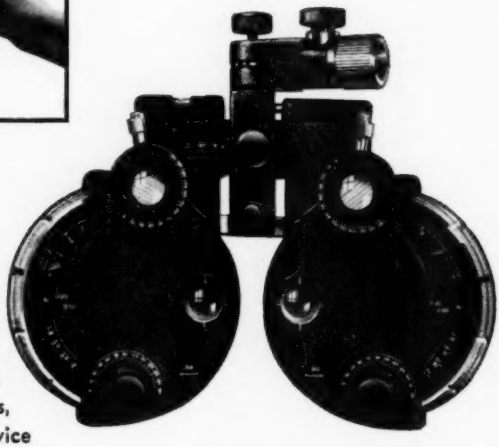

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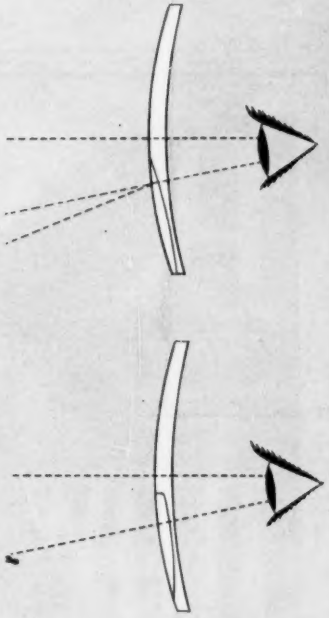

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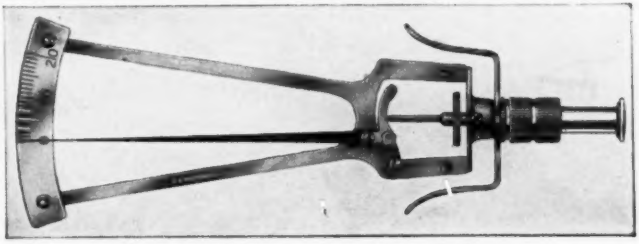

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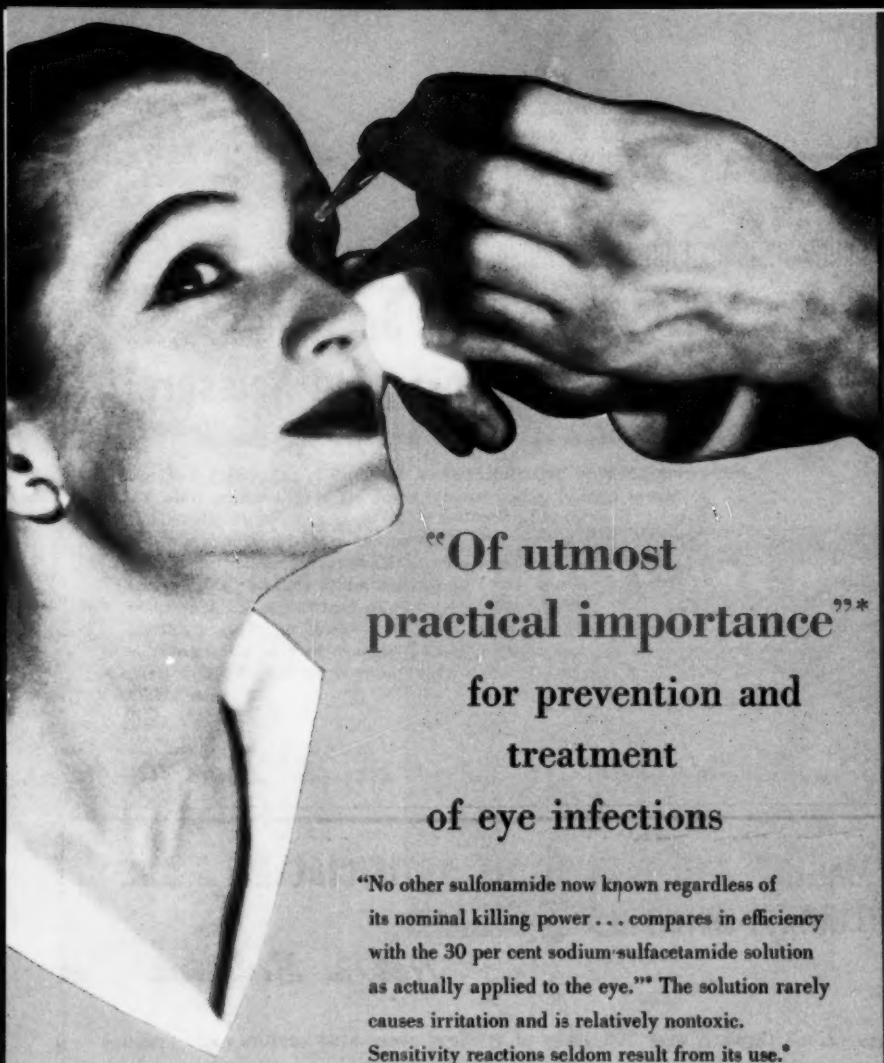

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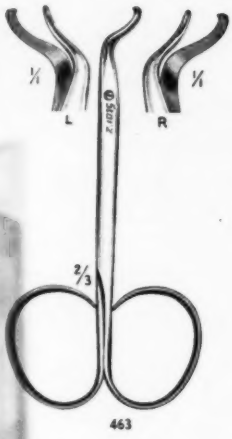

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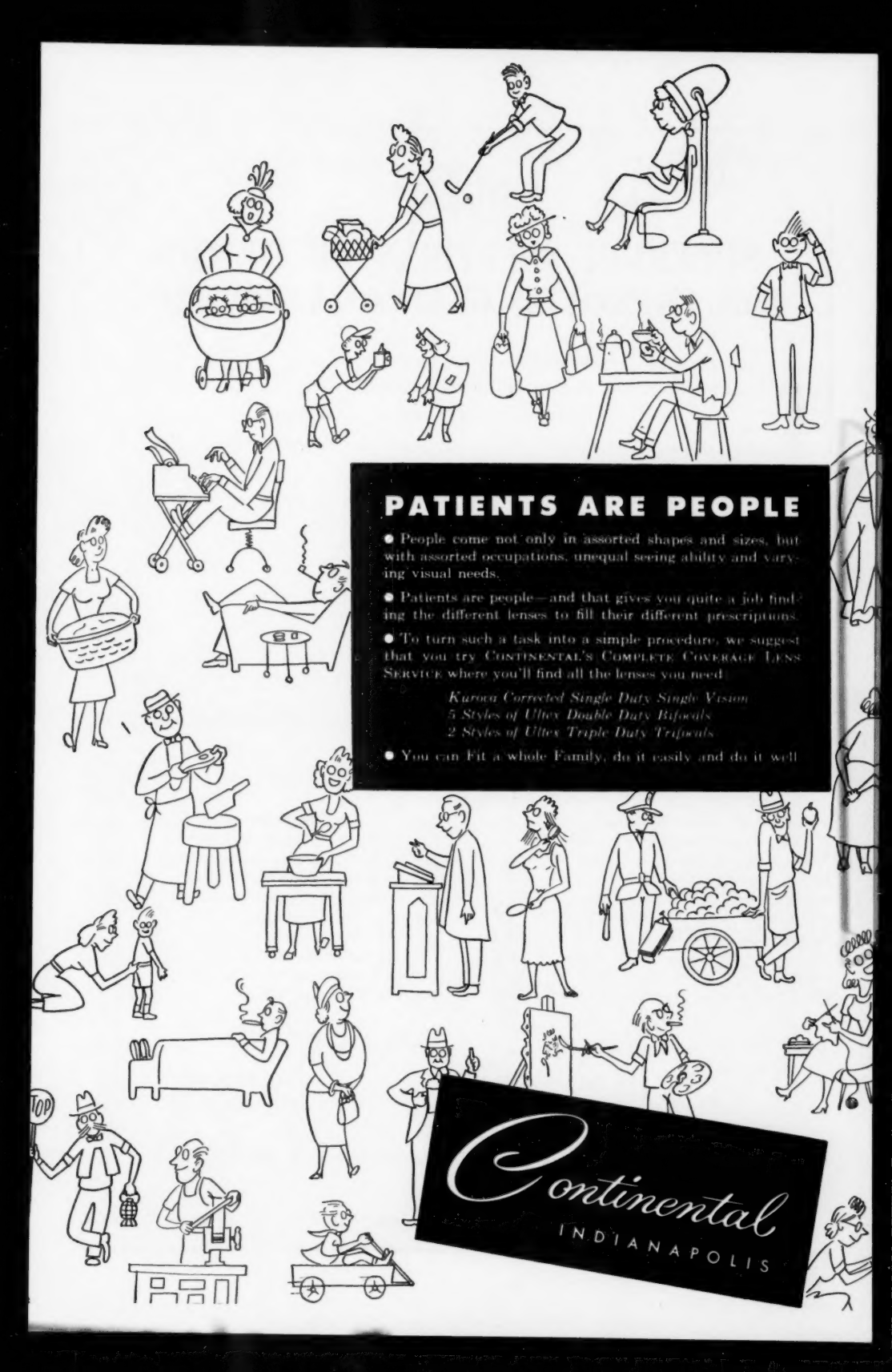
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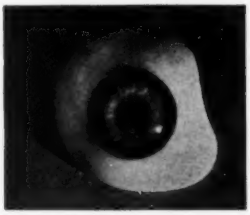

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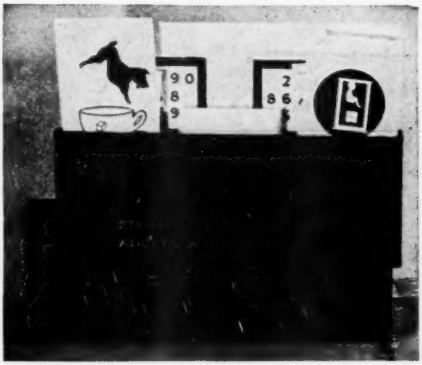

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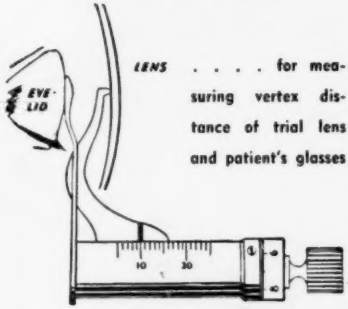

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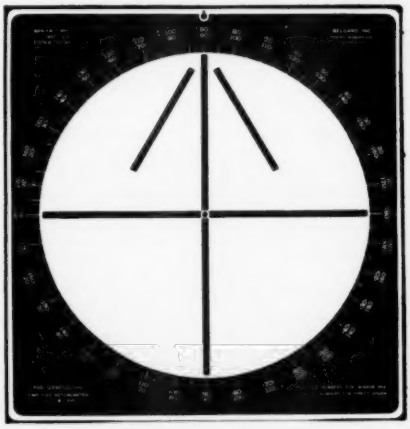

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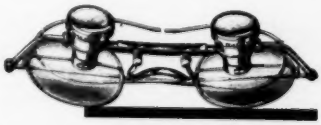

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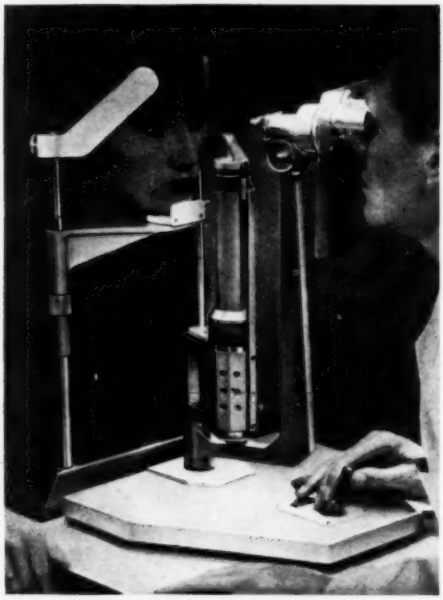

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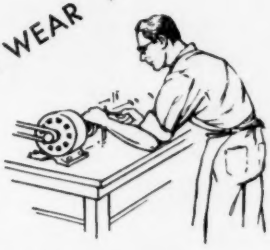

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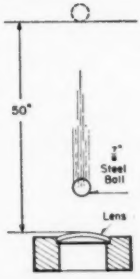

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TOXOPLASMA CHORIORETINITIS IN ADULTS

HELENOR CAMPBELL WILDER
WASHINGTON, D. C.

ORGANISMS morphologically indistinguishable from Toxoplasma have been found in chorioretinal lesions in 53 eyes in the Registry of Ophthalmic Pathology. Included in this group are 41 eyes mentioned in a preliminary report.[1] The patients were from 14 to 83 years of age at the time of enucleation, and, although eye symptoms had been observed for from a few weeks to 32 years, the earliest history of onset was at 12 years, in one instance. On the other hand, six patients had a history of onset in the seventh decade of life, and two, in the eighth. Thirty-seven patients were male; 15 were female, and the sex of one patient was unknown. The preponderance of males may be accounted for by the military source of much of the material examined. Forty-nine of the patients were white; 3 were Negroes, and 1 was a Filipino. The geographic distribution was wide. Specimens were sent in from all sections of the United States, and one patient was a resident of the Canal Zone. Three patients first noted symptoms while in the European theater and one while in the Pacific area. Thirteen patients gave a history of direct injury to the eye at varying intervals before enucleation, but in only three was the eye penetrated. All of the patients with penetrating injuries and seven of those with histories of nonpenetrating injuries related their symptoms to trauma, as did one other, who suffered a blow to the head shortly before the onset of ocular inflammation.

The patients were, on the whole, free from generalized symptoms which could be related to the ocular disease. However, one had a sore throat when chorioretinitis was first noted, and one, an inguinal-node lesion histologically similar to the ocular lesion. Concurrent with the eye symptoms, one patient had mild diabetes; two, rheumatoid arthritis and one gall-bladder attacks and heart decompensation. The eyes were usually blind and painful at the time of enucleation, although pain tended to be intermittent, rather than constant, and in two instances it was denied. In only three patients was there evidence of bilateral involvement: Scars of old chorioretinitis were noted in two, and active chorioretinitis was present in the third.

Specific clinical opinions had not always been submitted with the specimens, but in 37 cases the clinical diagnosis was uveitis, and in 9 of these the uveitis is known to have been regarded as tuberculous. Neoplasm was considered, usually in addition to uveitis, in 18 cases in which the fundus could not be observed or in which there were scleral nodules. Secondary glaucoma was present in 31 cases; hypotony, in 16, and in 6 the tension was normal. At the present time serum has been obtained

Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology.

1. Wilder, H. C.: Toxoplasma Chorioretinitis in Adults, A. M. A. Arch. Ophth. **47**:425, 1952.

from only three patients in whose eye lesions protozoa have been identified. Dye tests, as recommended by Sabin and Feldman,[2] have been performed in three cases. A dye-test titer of 1 : 64 was obtained on two patients, on one 2½ years and on the other 7 months after enucleation. In another whose eye had been enucleated six years earlier the dye-test titer was 1 : 256. Further serologic studies are in progress in collaboration with Dr. Leon Jacobs, of the National Institutes of Health, and Col. J. H. King Jr., Medical Corps, United States Army, Walter Reed Army Hospital.

The granulomatous character of the lesions with central necrosis had, in 30 eyes, led to a pathologic diagnosis of tuberculosis or possible tuberculosis. A pathologic diagnosis of syphilitic chorioretinitis had been made in three cases in which the

Fig. 1.—Granulomatous lesion involving retina and choroid, and forming an episcleral nodule. AFIP Acc. 70313; × 2.

patients' Wassermann reactions were positive. Twenty of the eyes studied for the first time after special interest in the characteristic lesion had been aroused had been diagnosed more evasively as granulomatous chorioretinitis, etiology undetermined.

The lesions in which the organisms were found were all strikingly alike and focally involved the retina, the choroid, and frequently the sclera. They were posterior, equatorial, or peripheral, and occasionally more than one lesion was present in a single eye. At the center of each lesion the retina was necrotic and had completely lost its normal architecture, retaining only a few parenchymal nuclei from which the normal chromatin pattern had disappeared. Bruch's membrane was interrupted. The stroma of the underlying choroid was either necrotic or replaced by epithelioid cells. Melanin granules from the necrotic retinal pigment epithelium

2. Sabin, A. B., and Feldman, H. A.: Dyes as Microchemical Indicators of a New Immunity Phenomenon Affecting a Protozoon Parasite (Toxoplasma), Science **108**:660-663, 1948.

Fig. 2.—Granulomatous lesion involving retina, choroid, sclera, and episclera. Necrosis of retina and choroid. AFIP Acc. 165904; × 48.

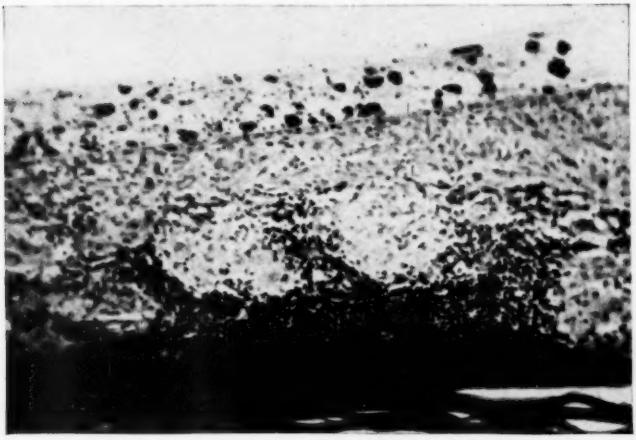

Fig. 3.—Necrosis of retina with scattering of melanin from pigment epithelium; epithelioid cells and lymphocytic infiltration in choroid. AFIP Acc. 171510; × 125.

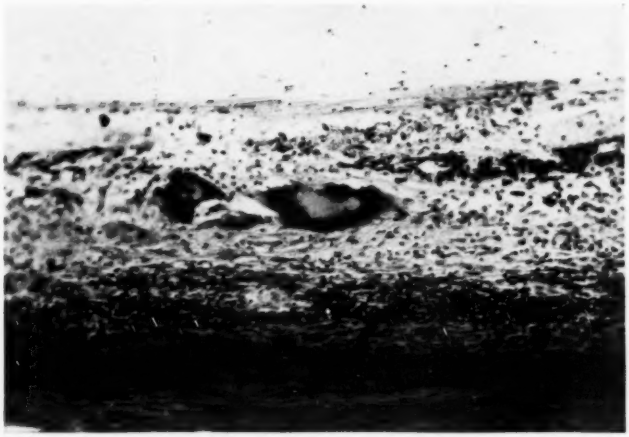

Fig. 4.—Giant cells containing phagocytosed pigment in chorioretinal lesion. AFIP Acc. 171510; × 125.

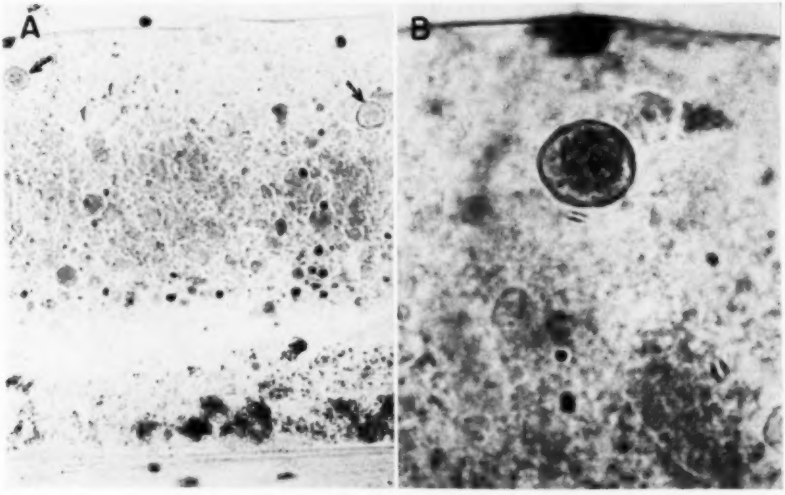

Fig. 5.—*A*, necrotic retina containing cystoid structures, possibly pseudocysts with dead organisms. AFIP Acc. 70313; × 355. *B*, cystoid structure with well-defined border, possibly pseudocyst containing dead organisms. AFIP Acc. 70313; × 1,260.

and the choroidal melanoblasts were generally phagocytosed by the epithelioid and giant cells. The necrotic central portion of the lesion was invariably surrounded by epithelioid cells, varying numbers of giant cells, lymphocytes, and plasma cells. Eosinophiles were nearly always present but usually were not prominent. The underlying sclera, and even the episclera, had frequently undergone nodular inflammatory thickening. Hemorrhages were sometimes present but in most instances were small, and usually in the form of minor extravasations of erythrocytes at the margins of the lesions. Polymorphonuclear leucocytes were occasionally seen, particularly in the areas of necrosis. Some eyes showed comparatively little inflammatory reaction apart from the primary lesion, but in many there was widespread inflammatory reaction, evidenced by non-necrotizing foci of epithelioid cells throughout the choroid and ciliary body. Sometimes similar foci were seen in the retina. Clumps of mononuclear cells often adhered to the inner surface of the retina, to the optic disk, and to the posterior surface of the cornea, and others were scattered throughout the vitreous. There was sometimes dense diffuse lymphocytic and plasma-cell infiltration in the iris, with lymphocytic periphlebitis in the ciliary body, choroid, retina, and nerve head. Occasionally keratitis was present. Cataract, secondary glaucoma, intraocular hemorrhage, retinal detachment, hypotony, and beginning atrophy of the globe were observed as complicating factors.

It was in the necrotic portion of the retina in the focal granulomatous chorioretinal lesions that the organisms were found. Crescentic forms were often arranged in pairs or rosettes, whereas spherical forms commonly occupied pseudocysts. The crescent-shaped organisms were characteristically rounded at one end and pointed at the other, with a rather large nucleus near the blunt end. Granules were sometimes distinguishable in the cytoplasm. In celloidin sections the organisms, according to micrometer measurements of extracellular crescentic forms, were from 3 to 5.3 μ in length, that is, within the limits specified by Cross [3] for Toxoplasma in smears of ascitic fluid from inoculated mice. There was no kinetoplast, as in Leishmania and Trypanosoma cruzi. The organisms were larger and more uniform in size and shape than Encephalitozoon, as described by Perrin.[4] In general, the cytoplasm stained uniformly in hematoxylin-and-eosin preparations. The pseudocysts were not subdivided, as are sarcocysts, nor did they attain as large a size. They were frequently clustered around the remaining nuclei of retinal cells. Round structures, which had well-defined borders and contained amorphous material, were often found in the necrotic retina. In routine hematoxylin-and-eosin sections both these structures and the surrounding necrotic retina took the eosin stain; with periodic acid-fuchsin the central material was reddish. The round structures were interpreted as possible pseudocysts containing dead organisms.

The morphologic features of the organisms were best preserved in celloidin sections. Because of greater shrinkage, crescentic forms were rarely demonstrated in paraffin sections, and round forms were often distorted and difficult to differentiate from nuclear debris. This is probably one reason why they have been overlooked for so many years. The organisms were beautifully demonstrated by hematoxylin-and-eosin staining; they were periodic acid-fuchsin-positive, but Gram-negative. In

3. Cross, J. B.: A Cytologic Study of Toxoplasma with Special Reference to Its Effect on the Host's Cell, J. Infect. Dis. **80**:278-296, 1947.

4. Perrin, T. L.: Toxoplasma and Encephalitozoon in Spontaneous and in Experimental Infections in Animals, Arch. Path. **36**:568-578, 1943.

Fig. 6.—Epithelioid cells and lymphocyte and plasma-cell infiltration in iris. AFIP Acc. 171510; × 75.

Fig. 7.—Epithelioid and giant cells in ciliary body. AFIP Acc. 482589; × 125.

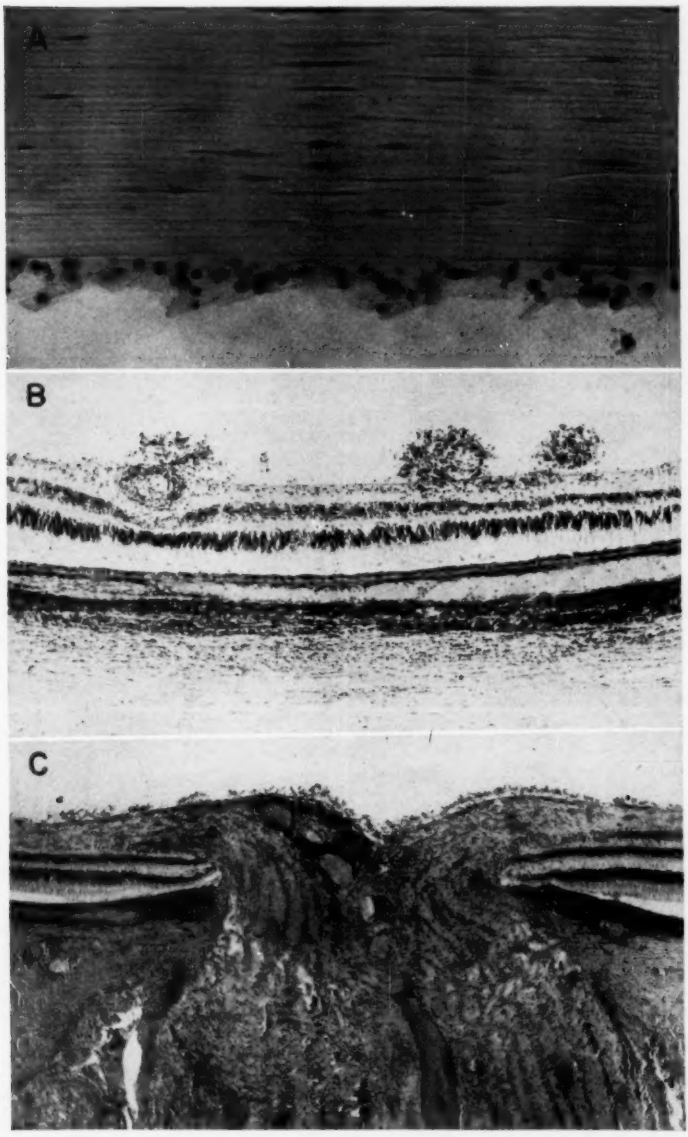

Fig. 8.—*A*, clumps of mononuclear cells on posterior surface of cornea. AFIP Acc. 70313; × 315. *B*, clumps of mononuclear cells on inner surface of retina, capping retinal vessels; lymphocytic periphlebitis in retina; lymphocytic infiltration of choroid. AFIP Acc. 37670; × 75. *C*, mononuclear cells on optic disk; lymphocytic periphlebitis, nerve head. AFIP Acc. 37670; × 45.

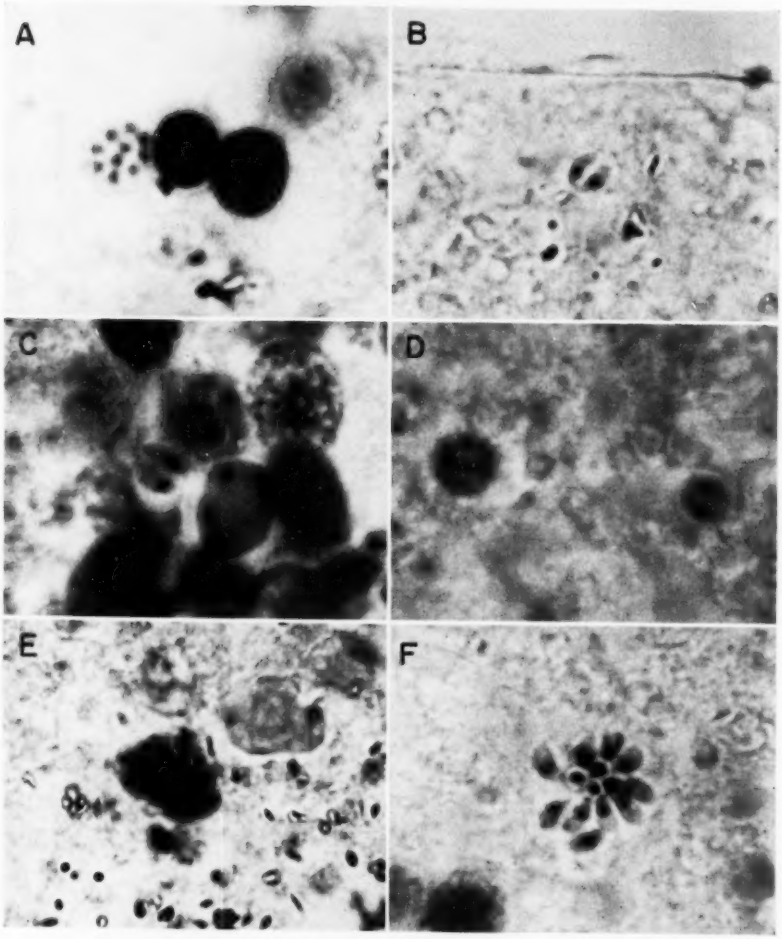

Fig. 9.—*A*, protozoa in pseudocyst near nuclei of retinal cells. AFIP Acc. 211318; × 3,600. *B*, crescent-shaped protozoa, paired, in necrotic retina. AFIP Acc. 211318; × 1,800. *C*, crescent-shaped protozoa surrounded by nuclei of retinal cells and ill-defined pseudocysts. AFIP Acc. 70313; × 2,160. *D*, pseudocyst containing round protozoa, left; free crescentic protozoa, right. AFIP Acc. 211318; × 3,600. *E*, pseudocyst with round protozoa. AFIP Acc. 70313; × 1,260. *F*, crescentic protozoa in rosette formation in necrotic retina. AFIP Acc. 165904; × 2,160.

approximately half the lesions they were easily found with the oil immersion lens. In the other half careful search was necessary. Several eyes had been prepared for teaching sets on tuberculosis, and 30 to 50 sections passed through a single lesion. In examining these microscopically it was found that at some levels the sections contained large clumps of organisms, whereas at others none were identified.

COMMENT

Although neither Toxoplasma nor Toxoplasma-like organisms have heretofore been demonstrated in chorioretinal lesions in adults, many investigators have made at least a tentative clinical diagnosis of Toxoplasma chorioretinitis on the basis of serologic tests. Frenkel [5] obtained 71% positive skin tests for Toxoplasma in patients with chorioretinitis and concluded that this parasite was a frequent cause of chorioretinitis in adults.

Vail, Strong, and Stephenson [6] gave a clinical description of chorioretinal lesions in six patients, ranging in age from 7 to 23 years, with positive neutralization antibodies for Toxoplasma. Their description was reconcilable with the pathologic pattern of the lesions discussed in this paper, although in the latter there was no special selectivity for the macular area. More recently Rieger,[7] on the basis of skin and serum tests, coupled with the similarity of the ocular lesions in his patients, made a diagnosis of Toxoplasma chorioretinitis in 14 adults. Although he regarded the Sabin-Feldman [2] dye test as specific for Toxoplasma gondii, he was not convinced that a negative dye test ruled out toxoplasmosis, particularly in old infections. On the other hand, Sabin [8] believed the demonstration of a high titer for toxoplasmic antibody to be of the utmost importance in the diagnosis of clinically acute, noncongenital chorioretinitis. He did not deny that acute chorioretinitis could occur in an adult as a result of toxoplasmic infection, but found no adequate proof for it. Hogan,[9] who gave an excellent review of the subject in his monograph "Ocular Toxoplasmosis," was unable on the basis of the rabbit neutralization test on adults with iridocyclitis and chorioretinitis to draw any conclusions as to the relationship between uveitis and toxoplasmosis. He found the incidence of positive dye tests, as well as titer, much as had been estimated for the same age group, i. e., 20 to 76 years, in the normal population.

Chorioretinitis, characteristically present in infants with congenital toxoplasmosis, has not been observed in adults dying of the acute, febrile form of the disease, reported first by Pinkerton and Henderson [10] and subsequently by Pinkerton and

5. Frenkel, J. K.: Uveitis and Toxoplasmin Sensitivity, Am. J. Ophth. **32**:127-135, 1949.

6. Vail, D.; Strong, J. C., Jr., and Stephenson, W. V.: Chorioretinitis Associated with Positive Serologic Tests for Toxoplasma in Older Children and Adults, Am. J. Ophth. **26**: 133-141, 1943.

7. Rieger, H.: Toxoplasmosis Acquired in Adult Life, Klin. Monatsbl. Augenh. **119**:459-476, 1951; A Further Report on Cases of Central External Exudative Retinitis Presumably Caused by an Acquired, Adult Toxoplasmosis, ibid. **120**:33-50, 1952.

8. Sabin, A. B.: Toxoplasmosis: Diagnosis and Treatment, Tr. Am. Acad. Ophth. **54**:190-204, 1950; Am. J. Ophth. **33**:1255-1268, 1950.

9. Hogan, M. J.: Ocular Toxoplasmosis, New York, Columbia University Press, 1951.

10. Pinkerton, H., and Henderson, R. G.: Adult Toxoplasmosis: a Previously Unrecognized Disease Entity Simulating the Typhus-Spotted Fever Group, J. A. M. A. **116**:807-814, 1941.

Weinman [11] and others.[12] Neither has chorioretinitis been observed in the asymptomatic mothers of infants with toxoplasmosis.

Heath and Zuelzer,[13] as well as Sabin,[8] suggested the possibility of protozoa similar to Toxoplasma, but with dissimilar antibody and pathogenic reactions, as causes of disease in man. Sabin pointed out that the hemogregarines may simulate Toxoplasma in birds and other animals.

Whether or not one is willing, on a morphologic basis, to accept as Toxoplasma the protozoa described in this paper, there would seem to be no doubt that they are a not uncommon cause of chorioretinitis in adults or that chorioretinitis, so often regarded as tuberculous, is, in many instances, due to a protozoon. In the Registry of Ophthalmic Pathology, among 131 eyes with the pathologic diagnosis of tuberculosis or possible tuberculosis, identical protozoa have been demonstrated in 30, whereas in only 3 have tubercle bacilli been found, although all the suspected lesions have been subjected to acid-fast staining and careful search.

SUMMARY

Organisms having the morphologic characteristics of Toxoplasma have been found in the necrotic retina in granulomatous chorioretinal lesions in 53 eyes of adults.

The lesions were strikingly uniform, and their appearance had in many instances led to a pathologic diagnosis of tuberculosis. They were in most cases unilateral, and the patients were usually without symptoms which could be related to their ocular disease.

11. Pinkerton, H., and Weinman, D.: Toxoplasma Infection in Man, Arch. Path. **30**:374-392, 1940.

12. Guimães, F. N.: Human Toxoplasmosis: Toxoplasmic Meningoencephalomyelitis; Occurrence in an Adult and in a Newborn Infant, Mem. Inst. Oswaldo Cruz **38**:257-320, 1943. Kean, B. H., and Grocott, R. G.: Asymptomatic Toxoplasmosis, Am. J. Trop. Med. **27**: 745-748, 1947.

13. Heath, P., and Zuelzer, W. W.: Toxoplasmosis: Report of Eye Findings in Twins, Arch. Ophth. **33**:184-191, 1945.

CEREBRAL ELECTRIC RESPONSE TO INTERMITTENT PHOTIC STIMULATION IN AMBLYOPIA EX ANOPSIA

A Preliminary Report

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IOWA CITY
AND
C. WESLEY WATSON, M.D.
With the Technical Assistance of Marjorie M. Edmond, B.A.
BOSTON

STATEMENT OF THE PROBLEM

AMBLYOPIA ex anopsia and the closely related phenomenon of suppression present problems which extend beyond purely ophthalmologic interest. In amblyopia and in suppression there has been provided a "natural" experimental situation in which a tissue showing no discernible pathologic change is affected by a reversible inhibition of its function.

Inhibition of function is a general property of the nervous system. In the case of more or less transient suppression of central vision in one eye and in amblyopia ex anopsia, a situation obtains in which one aspect of the inhibitory process is readily accessible to investigation in the intact human organism.

Some authors believe that the seat of the inhibition in amblyopia ex anopsia is in the retinal neurons; others are of the opinion that the seat is in the central nervous system. We incline toward the latter view, since a study of the dark-adaptation process in highly amblyopic eyes has indicated a perfectly normal response of the retina.[1]

It has occurred to us that electroretinography would offer another means of investigating retinal function in amblyopia ex anopsia. We have, accordingly, recorded simultaneously the electroencephalogram (cerebral potentials), the electro-

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Senior Fellow in Poliomyelitis, National Research Council, under a grant from the National Foundation for Infantile Paralysis (Dr. Watson).

Read at the meeting of the Eastern Division, Association for Research in Ophthalmology, Inc., Jan. 27, 1951.

From the Eye Service and the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School.

Supported by a grant to Dr. Burian by the Arnold Reuben Fight for Sight Fund of the National Council to Combat Blindness, Inc.

1. Wald, G., and Burian, H. M.: The Dissociation of Form Vision and Light Perception in Strabismic Amblyopia, Am. J. Ophth. **27**:950-963 (Sept.) 1944.

retinogram (retinal potentials), and the photic stimulus itself. The combined recording of these three phenomena was used by Monnier [2] in a somewhat different context.

Before proceeding with this part of the work, we felt it necessary to establish, if possible, what, if any, characteristic findings there are in the electroencephalogram of patients with amblyopia ex anopsia in relation to controlled and adequate stimulation of the retinal elements. The present paper is a brief report of the results of that investigation.

PREVIOUS INVESTIGATIONS

Callahan and Redlich [3] found a normal occipital rhythm in 10 patients with amblyopia ex anopsia and stated that "there was no difference in the occipital waves when the normal and when the amblyopic eye was stimulated in turn by a weak light, a bright light, by reading, and by reviewing a picture." It would seem from this statement that there was no lateralized abnormality in the records of the patients whom Callahan and Redlich examined, but the statement is too brief and lacking in the description of experimental details to permit a closer discussion.

Dyer and Bierman [4] have studied only spontaneous changes in cortical potentials in amblyopia ex anopsia. They examined 33 patients with amblyopia ex anopsia between the ages of 4 and 14 years and 5 such patients between the ages of 17 and 30 years. Of the 28 children, 24 had tracings which the authors considered to be abnormal; of the tracings of the 5 adults, that of only 1 was thought to be abnormal.

The abnormality found by the authors consisted, apparently, mainly of bursts of high-amplitude slow waves with interspersed low-amplitude fast activity. They recorded only when the patients had their eyes closed, thus excluding any visual stimulation.

There is by no means full agreement among encephalographers as to what constitutes a "normal" electroencephalogram, and, especially in children, occurrences such as those found by Dyer and Bierman are by no means rare. In the absence of adequate controls, it is extremely difficult to evaluate the findings reported briefly by these authors. In any event, their findings are related to various types of mixed activity of the whole cortex, without mention of important relationships of controlled adequate stimulus, laterality of stimulus, and characteristics of the cerebral response.

MATERIALS

Sixty-five normal subjects and 23 patients with amblyopia ex anopsia were investigated.[5] The ages of the patients varied from 4 to 35 years. The intensity of the amblyopia varied from an insignificant degree (20/30) to very deep amblyopia (20/200, with eccentric fixation). Some of the affected persons had been treated by occlusion prior to the test, while others had had no treatment.

2. Monnier, M.: L'électro-rétinogramme de l'homme, Electroencephalog. & Clin. Neurophysiol. **1**:87-109 (Feb.) 1949.

3. Callahan, A., and Redlich, F. C.: Electroencephalography and Ophthalmology, Am. J. Ophth. **29**:1522-1533 (Dec.) 1946.

4. Dyer, D., and Bierman, E. O.: Cortical Potential Changes in Amblyopia ex Anopsia: A Preliminary Report, Am. J. Ophth. **33**:1095-1098 (July) 1950.

5. Between the end of January, 1950, when this paper was read, and June 1, 1951, 6 additional "normal" persons and 32 additional patients with amblyopia ex anopsia were tested.

METHODS

Records of cerebral electrical activity were made on a Grass standard ink-writing electroencephalograph with measured occipital-central scalp electrode placements, under the conditions indicated on the Figures. An additional channel attached to a photoelectric cell provided a record of the light stimulus.

The subjects were seated in an electrically grounded, shielded cage covered with opaque cloth, permitting complete darkening or diffuse lighting, as required.

Recordings were made with eyes closed (light through lids) and opened, and with alternate opening and closing of the eyes, in the dark, as well as in diffuse light. This established a standard situation prior to test stimulation with high-intensity stroboscopic light (Strobolux, General Radio Co.). The flashes in these experiments varied in frequency from one to four flashes per second [6] and were evenly spaced.

Both eyes were first exposed to the flashing light; then alternately the right and the left. Between each of these exposures the nonexposed eye was closed and covered with a light-tight cover. Special attention was given to the matter of fixation. One of us was always present in the cage with the patient, watching his eyes closely and exhorting him to keep fixation on the center of the flashing filament.

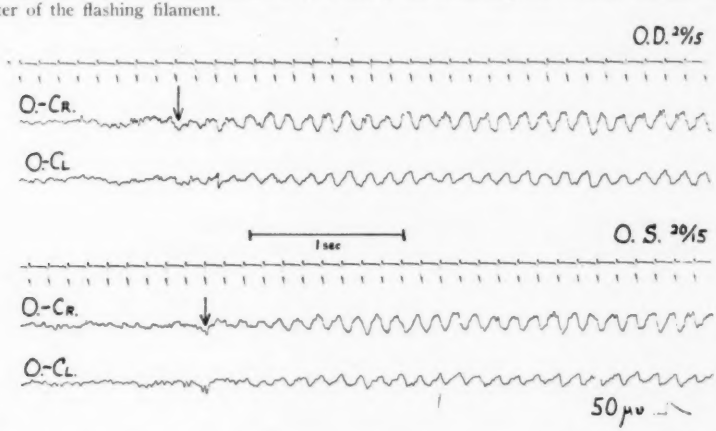

Fig. 1 (P. K., aged 35).—Normal eyes; normal nervous system. Prominent photic driving, both hemispheres, with exposure of either eye to light (arrow). Light stimulus indicated in first channel in all figures. Cerebral electrical activity in second and third channels. Occipital-central electrode placements in all figures: O–C_R, right hemisphere; O–C_L, left hemisphere. (Note that photic driving here resembles alpha activity, but is easily distinguished by the fixed relation of each of the waves to the preceding light-flash stimulus.)

RESULTS

It has long been known that opening the eyes, in the dark, as well as in the light, results in "blocking" of the so-called alpha waves.[7] In previous control studies we have established, however, that well-defined alpha rhythm may be resumed with eyes open in the light under certain conditions of subjective "recall."[8] Knowing this, we have used alternate exposure of eyes in repeated sequence, thus establishing a control in the same subject.

6. In later tests, higher frequencies (up to 19 flashes per second) were also employed.

7. Alpha rhythm is roughly defined as a rhythm of about 10 cps (8 to 13 cps) occurring in the parieto-occipital areas and usually attenuated by physiologic stimuli (Hill, J. D. N., and Parr, G.: Electroencephalography: A Symposium on Its Various Aspects, New York, The Macmillan Company, 1950, p. 381).

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It has also been known for some time that rhythmic illumination of the eyes may result in a rhythmic electric response from the occipital cortex. This phenomenon is known as "photic driving."

Beyond the basic fact of its existence, relatively little is known about photic driving. In order to learn more about it at first hand and to obtain controls for the study of amblyopic patients, 65 persons considered normal from the ophthal-

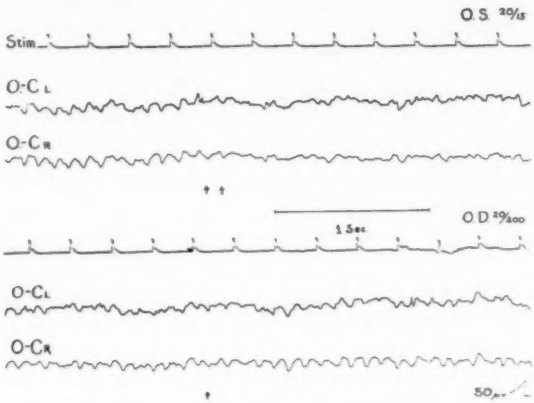

Fig. 2 (H. F. B., aged 35).—Immediate alpha blocking when left eye was exposed to flashing light (arrow). No alpha block when amblyopic (right) eye was exposed (arrow).

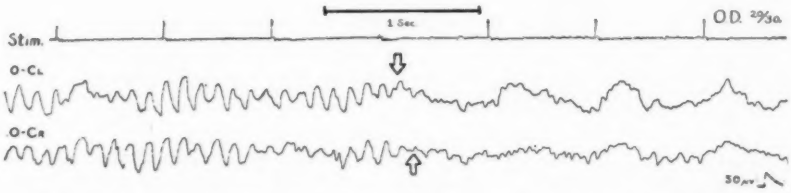

Fig. 3 (J. H. Jr., aged 2 years).—Alpha blocking by exposure of right eye to light (arrow) in spite of slight amblyopia.

mologic and neurologic standpoint were investigated.[6] The data obtained led to the following general observations germane to the present study:

1. In normal photic driving there corresponds to a series of light stimuli falling on the retina a series of electric responses from the occipital region, having a latency of approximately 90 msec. with respect to the stimulus light (Fig. 1).

2. Not every normal subject shows photic driving.

3. Optimum photic driving is not achieved in all persons with the same stimulus frequency.

4. Fixation of and accommodation on the light source are of vital importance in the production of photic driving. The corollary of this finding is that the absence of photic driving bilaterally may have no significance other than to indicate faulty fixation or accommodation.

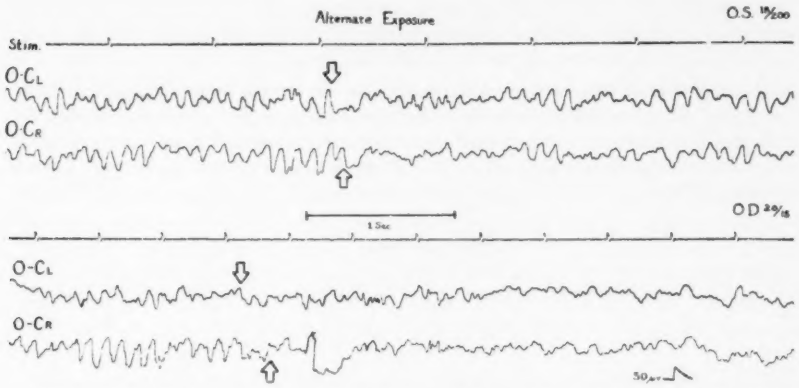

Fig 4 (E. B., aged 12).—Temporary blocking of alpha activity when amblyopic (left) eye was uncovered (arrow). Sustained blocking of alpha activity when right eye was uncovered (arrow).

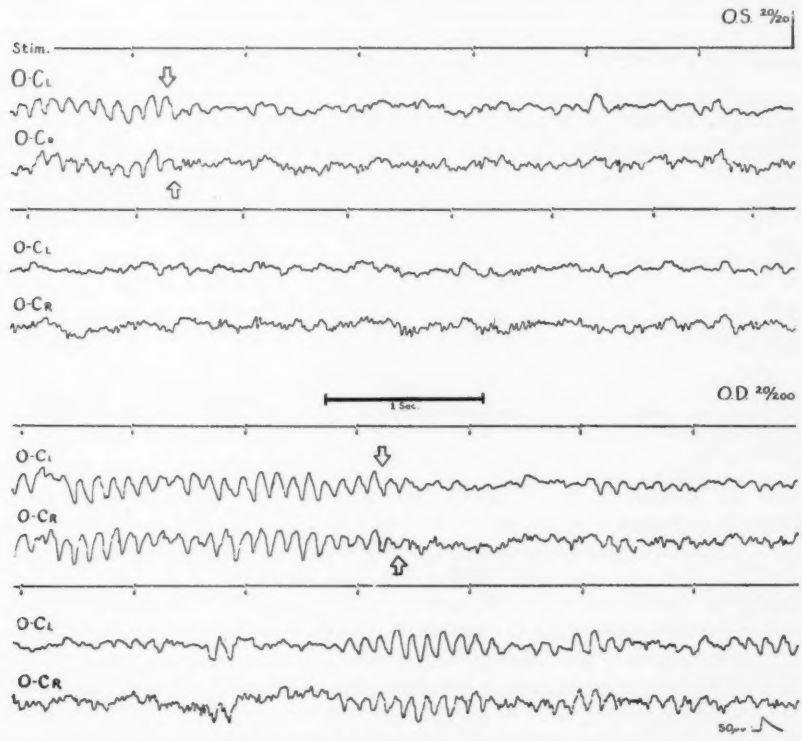

Fig. 5 (P. M., aged 14).—Sustained blocking of alpha activity when left eye was uncovered. Temporary blocking of alpha activity when amblyopic (right) eye was uncovered.

In the study of patients with amblyopia ex anopsia, we were primarily concerned with the two complex cerebral phenomena, alpha rhythm and photic driving. Our findings in these patients can be summarized as follows:

1. In some patients with severe amblyopia, we found that no suppression or "blocking" of alpha activity occurred when the amblyopic eye alone was stimulated with light flashes, while stimulation of the normal eye alone resulted in immediate suppression of alpha activity, which remained absent until both eyes were closed and covered (Fig. 2). In patients with a low degree of amblyopia this phenomenon

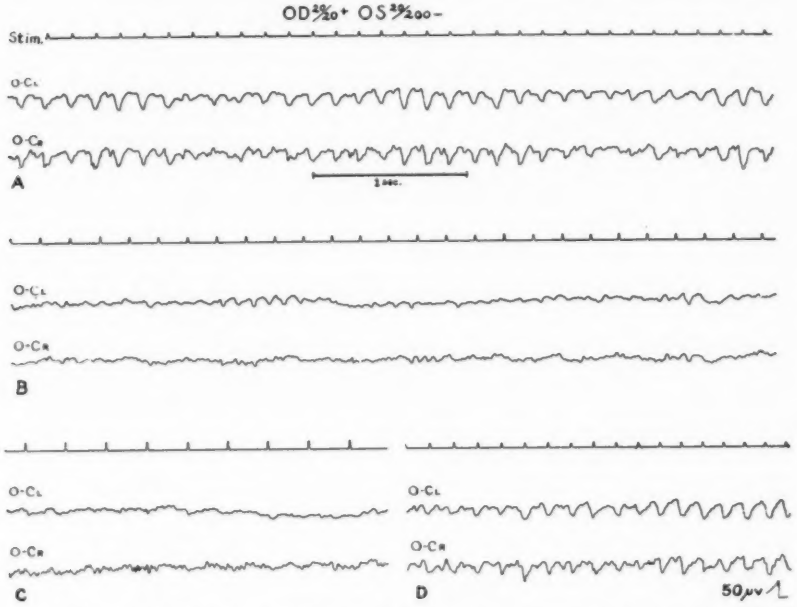

Fig. 6 (G. M., aged 34).—*A*, prominent bilateral cerebral response ("photic driving") when both eyes were exposed to intermittent light flashes. *B*, lack of cerebral response and appearance of alpha activity during exposure of amblyopic (left) eye. *C*, lack of cerebral response when both eyes were covered. *D*, prominent cerebral response without alpha activity when normal (right) eye was exposed to intermittent light flashes.

was not observed (Fig. 3). Thus, the degree of alpha blocking was roughly inversely proportional to the degree of amblyopia.

2. In some patients the alpha activity was at first blocked when the amblyopic eye was exposed to the stimulus of light, but it soon returned and remained present during the stimulation of the amblyopic eye (Figs. 4 and 5). Illumination of the normal eye did not produce this pattern of cerebral response.

3. Photic driving was found to be less easily produced through stimulation of amblyopic eyes. A comparison of the photic driving from the amblyopic and from the normal eye of the same patient showed that the cerebral response was less regular, often occurred momentarily, and was of lower voltage when the amblyopic eye was stimulated by light than when the normal eye was exposed (Fig. 6).

4. In patients in whom some photic driving could be elicited by illuminating the amblyopic eye, photic driving was often combined with alpha activity, an occurrence not seen in the normal eye (Fig. 6*B*).

It is our impression from these findings that there is a significant difference in cerebral response when the normal eye and when the amblyopic eye of the same subject are alternately exposed to intermittent stimulation with light, provided the amblyopia is deep enough (acuity, 20/70 or less). This would place the seat of the defect in the hemispheres rather than in the retina. But we also believe that a discussion of the significance of the positive results would be premature until more information is available about possible differences in the response from the two hemispheres and about the responses in both the electroretinogram and the electroencephalogram recorded simultaneously. Such correlative studies are in progress.

SUMMARY

Changes in the electroencephalogram in relation to a lateralized controlled and adequate stimulus of the retinal elements were noted in patients with amblyopia ex anopsia. The main electroencephalographic findings were as follows:

1. If the visual acuity of the amblyopic eye was 20/70 or less, alpha activity continued when the amblyopic eye was exposed to stroboscopic light stimulation, whereas it was immediately suppressed on exposure of the normal eye.

2. The rhythmic electric response from the occipital cortex in response to rhythmic illumination of the eyes ("photic driving") was less easily produced in some amblyopic eyes. The driving obtained by illuminating amblyopic eyes was less regular, often occurred momentarily, and was of lower voltage than that obtained by illuminating the normal, fellow eyes.

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COMPARISON OF RESULTS OF CORTISONE TREATMENT BY INSTILLATION AND BY SUBCONJUNCTIVAL INJECTION

An Experimental Study

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AS TOPICAL therapy for diseases of the cornea, cortisone is frequently given, either by instillation or by subconjunctival injection. Among the effects which cortisone may have on the diseased cornea is the inhibition of new vascularization. For this there is clinical evidence (Lepri,[1] Olson and others,[2] Steffensen and others,[3] Barrios and Barrière,[4] Thygeson and Fritz,[5] Arruga,[6] Scheie and others,[7] Fitzgerald and others,[8] Leopold and others,[9] Woods,[10] and Duke-Elder [11]) and experimental proof (Jones and Meyer,[12] Ashton, Cook, and Langham,[13] Lister and Greaves,[14] and Michaelson [15]). Provided a precise method of measuring new vascularization is used, the effect of cortisone given as drops may be compared with that of the drug injected subconjunctivally in inhibiting new-vessel formation. The method described by Campbell and Michaelson [16] (1949) appears to be precise enough for the present purpose and was used in the present investigation. The relative efficacies of instillation and of subconjunctival injection in controlling new vascularization can be taken as an index of their relative efficacies in diseases of the cornea that are influenced by cortisone.

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METHOD

The method used has already been described in detail (Campbell and Michaelson[16]). The experiment was carried out with 14 rabbits of various weights. After the instillation of a few drops of 1% tetracaine hydrochloride into the conjunctival sac, a standard lesion of the cornea was produced by the application of a platinum-wire cautery, supplied with a constant voltage and applied for a constant time. The lesion was placed in the 12-o'clock meridian with its center 2 to 2.5 mm. from the limbus, as well as could be judged. The ulcers were recauterized each day, the same cautery, heated by the same voltage, being used. In each animal both corneas were cauterized. All the right eyes received 2.5 mg. of cortisone acetate injected subconjunctivally close to the limbus in the 12-o'clock meridian. This dose was given three times at spaced intervals during the 10-day period of the experiment. The left eyes received instillations of cortisone acetate drops (5 mg. per milliliter), prepared from the commercial (Merck) suspension, 1 drop being instilled seven times a day during the 10-day period.

*Results of Instillation and of Subconjunctival Injection of Cortisone on New Vascularization of Standard Lesions of the Cornea**

	Eyes (Left) Treated with Instillation of Cortisone Drops (5 Mg. per Ml.)					Eyes (Right) Treated with 2.5 Mg. of Cortisone as Subconjunctival Injection				
Rabbit No.	Ulcer-Limbus Distance	Base of Vascular Area	Height of Vascular Area	Size of Ulcer	Extent of Vascular Area	Ulcer-Limbus Distance	Base of Vascular Area	Height of Vascular Area	Size of Ulcer	Extent of Vascular Area
1	2.1	4.0	0.8	1.3	1.6	2.4	3.5	0.8	1.3	1.4
4	2.0	4.0	1.2	1.3	2.4	2.3	3.0	1.3	1.3	2.0
6	2.0	4.0	1.3	1.0	2.6	2.0	5.0	1.0	1.0	2.5
8	2.5	4.0	1.0	1.0	2.0	2.0	2.8	2.0	1.3	2.8
9	2.1	5.0	1.5	1.3	3.8	1.9	5.0	1.9	1.3	4.8
10	2.5	4.0	1.0	1.4	2.0	2.0	5.0	1.5	1.2	3.8
11	2.0	4.0	1.2	1.3	2.4	2.3	3.0	1.0	1.3	1.5
13	1.8	5.8	1.8	1.3	5.2	2.3	4.5	1.5	1.3	3.4
14	2.5	5.0	1.5	1.3	3.8	2.5	6.0	1.3	1.3	3.9
5	2.0	3.0	0.05	1.3	0.8	1.9	3.0	0.05	1.0	0.8†
12	2.5	3.0	0.05	1.1	0.8	2.0	3.0	0.05	1.0	0.8†
2		Unsatisfactory injection					Unsatisfactory injection			
3		Unsatisfactory injection					Unsatisfactory injection			
7		Unsatisfactory injection					Unsatisfactory injection			

* All measurements are given in millimeters.
† Animal died between the second and the third day.

At the end of the serial cauterization the animals received a terminal injection of "pro-dorm" (a combination of barbiturates), and India ink was injected under pressure into the carotid arteries, 10 to 15 ml. of the ink being given into each carotid artery under a pressure of 100 to 150 mm. Hg. Immediately prior to the injection as much as possible of the aqueous fluid was removed from the anterior chamber by means of a syringe. This procedure appeared to facilitate the injection of the corneal vessels. The eyes were excised and placed in 10% formalin for 24 hours. The appropriate portion of the cornea was then excised and mounted in glycerin. The vascular area was measured with the micrometer of a microscope eyepiece. The following measurements were made in each case: size of ulcer; distance between ulcer and limbus; area of triangle of new vascularization.

RESULTS

These results are given in the accompanying table..

It will be noted that in three animals the injection was unsatisfactory, and the results obtained were discarded. Two animals (Rabbits 5 and 12) died between the second and third days of the experiment. The results in these animals will be considered separately. The results obtained in the nine remaining animals will now be considered.

Size of Ulcer.—Nine eyes were treated by instillation of drops. The mean size of the ulcer was 1.2 ± 0.14 mm., the range being 1.0 to 1.4 mm.

Nine eyes were treated by subconjunctival injections. The mean size of the ulcer was 1.3 ± 0.10 mm., the range being 1.0 to 1.3 mm.

Distance of Ulcer from Limbus.—Nine eyes were treated by instillation of drops. The mean distance was 2.2 ± 0.25 mm., with a range of 1.8 to 2.5 mm.

Nine eyes were treated by subconjunctival injections. The mean distance was 2.2 ± 0.20 mm., with a range of 1.9 to 2.4 mm.

With respect to the size of the ulcer and the distance from ulcer to limbus, it would appear that the two groups are sufficiently similar to permit comparison of the right eyes, treated with subconjunctival injections, and the left eyes, treated with instillation of the agent.

Extent of Areas of Vascularization.—Nine eyes were treated by instillation of drops. The mean extent was 2.9 ± 1.1 sq. mm., the range being 1.6 to 5.2 sq. mm.

Nine eyes were treated with subconjunctival injections. The mean extent was 2.9 ± 1.1 sq. mm., the range being 1.4 to 4.8 sq. mm.

The results are highly significant of the similarity of action on corneal vascularization of cortisone given by instillation and cortisone injected subconjunctivally.

The area of vascularization produced by an experimental lesion of the cornea is dependent on the distance of the lesion from the limbus. The areas of vascularization were, therefore, divided into those resulting from lesions situated 1.8 to 2.0 mm. from the limbus and those resulting from lesions situated 2.1 to 2.5 mm. from the limbus.

Extent of Vascularization When Ulcer Was 1.8 to 2.0 Mm. from Limbus: Four eyes were treated by instillation of drops. The mean extent was 3.2 sq. mm., the respective valves being 2.4, 2.4, 2.6, and 5.2 sq. mm.

Four eyes were treated by subconjunctival injections. The mean extent was 3.5 sq. mm., the respective values being 2.5, 2.8, 3.8, and 4.8 sq. mm.

Extent of Vascularization When Ulcer Was 2.1 to 2.5 Mm. from Limbus: Five eyes were treated by instillation of drops. The mean extent was 2.6 sq. mm., the respective values being 1.6, 2.0, 2.0 3.8, and 3.8 sq. mm.

Five eyes were treated by subconjunctival injection. The mean extent was 2.4 sq. mm., the respective values being 1.4, 1.5, 2.0, 3.4, and 3.9 sq. mm.

The similarity of the effect of instillation and that of injection is confirmed by this analysis. The distance of the ulcer from the limbus does not influence the relative efficacies of the two methods of application.

Early Effects of the Two Methods.—The deaths of Rabbits 5 and 12 between the second and third days after the initial cauterization gave an opportunity for comparison of the early effects of the two forms of treatment.

Method	Areas of Vascularization in Rabbit 5, Sq. Mm.	Area of Vascularization in Rabbit 12, Sq. Mm.
Eye treated with drops	0.8	0.8
Eye treated with injection	0.8	0.8

It appears that the two methods of topical application have equal effects from the onset of development of the new vascularization.

COMMENT

The method of measuring the extent of corneal vascularization employed in this study has already been used in a previous one, which showed that subconjunctival injections of cortisone reduced the extent of the standard vascular area by about 45% (Michaelson [15]). In that study 1.25 mg. of cortisone was injected subconjunctivally. The present investigation was designed to place the onus on the instillation method to prove a similar efficacy. For that reason, 2.5 mg. of cortisone was used for the subconjunctival injection, and the drops for instillation contained 5 mg. of cortisone per milliliter, which is about the weakest concentration employed in clinical treatment. The results show that instillation is as efficacious as subconjunctival injection in inhibiting new-vessel growth in the cornea. The effect of 1.25 mg. of cortisone given subconjunctivally is very similar to the effect of twice that dose given subconjunctivally, and it therefore is not likely that instillation of a concentration of cortisone greater than 5 mg. per milliliter will have much greater efficacy.

The degree of the effect of instillation on new vascularization may be taken as a measure of its effect on such corneal conditions as are influenced by cortisone.

SUMMARY AND CONCLUSIONS

In the corneas of rabbits, areas of new vascularization were produced by a standard method over a 10-day period.

The right eyes were treated with three subconjunctival injections of 2.5 mg. of cortisone acetate; the left eyes, with seven daily instillations of drops of the drug in the strength of 5 mg. per milliliter during the 10-day period.

The extents of the areas of new vascularization were similar in the right and in the left eyes, both at the onset and at the termination of the 10-day period.

Cortisone seems to be as effective in the treatment of corneal conditions when instilled as drops into the conjunctival sac as when injected subconjunctivally.

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Miss Ilana Moinester gave technical assistance.

CLINICAL EVALUATION OF THE AQUEOUS-FLOW TEST

A Preliminary Report

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THE GREAT number of provocative tests used in the diagnosis of glaucoma is itself an indication that none of them is entirely adequate. Therefore we regarded Grant's [1] aqueous-flow test with considerable interest, since it appeared to be a useful and efficient method of helping in the diagnosis of glaucoma. In an attempt to evaluate the role of this new approach to the problem of glaucoma, we undertook the present study.

METHOD

The theory and the technique of this test have been extensively discussed by Grant [2] and Friedenwald [3]; it is sufficient, therefore, to mention them only briefly. We followed Grant's method and employed either the five-minute or the abbreviated, four-minute, test with a recording galvanometer. We measured the facility of aqueous outflow (cubic millimeters per minute) on 400 eyes of 301 patients, performing 500 tests over a one-year period (December, 1950 to December, 1951). Most of the patients were obtained from the Vanderbilt Clinic; others were private patients of various staff physicians of the Institute of Ophthalmology.

RESULTS

Normal Subjects.—One-hundred-sixty tests were carried out on 140 normal eyes. The facility of aqueous outflow ranged from 0.100 to 0.523 cu. mm. per minute, with an average of 0.244 cu. mm. of aqueous per minute, per millimeter (Hg) of the intraocular pressure. The net rate of flow, which is also interpreted as the net rate of aqueous formation, ranged from 1.05 to 9.3 cu. mm., with an average of 4 cu. mm., per minute. The accompanying scattergrams (Charts 1 and 2) show that neither age nor sex had an appreciable effect on these values.

Primary Glaucoma.—Wide-Angle Chronic Simple Glaucoma (112 eyes): Forty-eight determinations were made on glaucomatous eyes of this type which had not been treated medically or surgically. The average value for the facility of outflow was 0.101 cu. mm. per minute, and the average total rate of flow was 2.29 cu. mm. per minute. With miotic therapy both these values improved.

From the Institute of Ophthalmology of the Presbyterian Hospital, New York.

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Narrow-Angle, Congestive Glaucoma (33 eyes): Without medication and between attacks, the average facility of outflow in 23 tests on glaucomatous eyes of this type was normal, i. e., 0.202 cu. mm. per minute, and the total rate of flow was 3.18 cu. mm. per minute.

Operative Results: In 20 eyes with narrow-angle glaucoma on which some sort of operation for glaucoma was done, the average facility of outflow was 0.228 cu. mm., and the average total rate of flow 3.66 cu. mm., per minute. For 34 eyes with wide-angle glaucoma on which operation had been performed the average values were 0.142 and 2.79 cu. mm., respectively, per minute. From these results it is apparent that both the facility of outflow and the total rate of flow were well within the normal limits postoperatively in most of the eyes with narrow-angle glaucoma while in eyes with the wide-angle type the improvement was less pronounced. About half these postoperative eyes received, and half had no, medication. As far as we could determine, the use of miotics after operation did not influence the aqueous-flow test.

Glaucoma Suspects.—As of this date, 25 eyes of 16 patients are still carried under this classification, for various reasons. Twenty-eight tests were done on these

Aqueous-Flow Tests on Patient with Early Wide-Angle Glaucoma (R. L.) and a Normal Subject (M. C.)

Patient	Sex and Age	Date (1951)	Eye	Facility of Aqueous Flow, Cu. Mm.	Total Rate of Flow, Cu. Mm.	Intra-ocular Pressure, Mm.	Medication
R. L.	F Young	6/18	O.D.	0.16	4.36	27.3	None
		9/17	O.D.	0.637	18.4	29.6	None
		10/ 2	O.D.	0.327	11.4	34.9	None
		10/ 2	O.S.	0.745	20.4	27.3	None
		12/17	O.D.	0.256	7.4	28.9	None
		12/17	O.S.	0.261	5.9	22.6	None
M. C.	F Middle-aged	4/12	O.S.	0.591	13.6	23.1	None

patients; and while both the facility of outflow and the total rate of flow were within normal limits in most instances, all these patients showed clinical signs of glaucoma or glaucoma-like disease, yet not enough evidence to permit diagnosis of the condition with assurance. Because of the suspicious clinical behavior of these eyes, and in spite of their normal or near-normal rates of aqueous flow, we believe it advisable to consider these eyes as suspect.

Secondary Glaucoma.—Nine of 10 eyes with secondary glaucoma due to cataract extraction showed a lower than normal rate of aqueous flow in spite of miotic therapy, although the tension was normal in 7 of these eyes. After uveitis, one patient with secondary glaucoma had normal values for aqueous flow without medication, while another showed considerable improvement with miotics.

Pseudoglaucoma.—Of two patients with this disease, one showed subnormal values in spite of miotic therapy, while the other had a normal aqueous flow without any medication.

Miscellaneous Types.—In this group we include a few cases in which tests gave baffling, and as yet not understandable, results. For example, R. L., who presented clinical evidence of early wide-angle glaucoma, had a very high facility of aqueous outflow and total rate of flow on repeated tests (Table). M. C., known to have normal eyes, and whose intraocular pressure was 27.0 mm., showed similar results,

COMMENT

Charts 1 and 2 show that the facility of aqueous outflow and the net rate of flow for the normal eyes varied considerably. However, at no time was the facility of outflow less than 0.1 cu. mm. In the range of values, our normal patients varied more than those reported by Grant, but we agree with him that the lower limit for the facility of outflow is about 0.1 cu. mm. per minute. At the beginning of our studies we were uncertain as to the dividing line between the values for normal and the values for glaucomatous eyes, and the more data we accumulate, the more it appears that there is no sharp line of demarcation. A small number of cases fall in a zone between the two groups, and we hope that further experience will help us to narrow this zone.

The results shown above demonstrate that, by and large, eyes with untreated wide-angle type of glaucoma have a lower than normal facility of aqueous outflow.

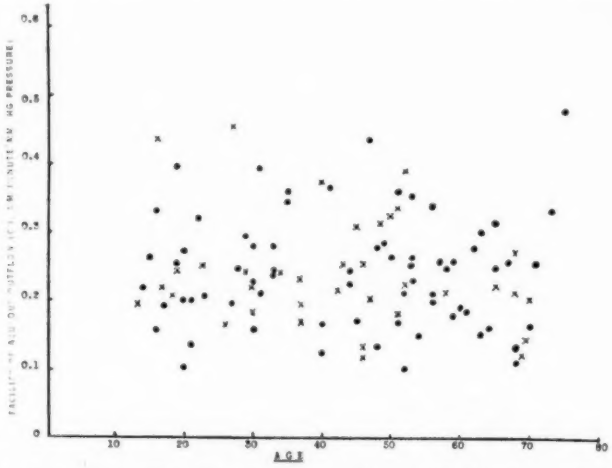

Chart 1.—Aqueous-outflow tests on 105 normal eyes, showing the relation between the facility of outflow and the age and sex of the subject.

In this chart and in the accompanying charts, values for females are indicated by black circles; values for males, by crosses.

However, we should like to point out that some of the untreated eyes with wide-angle glaucoma had normal aqueous flow. It is interesting to note that none of the values for normal eyes fell in the range for glaucomatous eyes. This is illustrated in Chart 3. This overlap of values for the normal and for the glaucomatous eyes was apparently not experienced by Grant, who reported a sharp line of demarcation. Miotic therapy improved both the facility of aqueous outflow and the total rate of flow for many of these eyes with wide-angle glaucoma, a typical case of which is shown in Chart 4. Pilocarpine was the miotic of choice in 95% of these cases. Since the full duration of the effect of this drug is not known, we arbitrarily decided that at least two days should pass after the last application before we could consider the eye free of medication. In order to explain the so-called "late effects" of pilocarpine medication, future research concerning the penetration into the eye and its duration of action seems warranted.

When the results of the aqueous-flow test were compared with the tension in eyes with wide-angle glaucoma, it was found that miotic medication lowered the tension to normal in about 80% of the cases, but brought the aqueous flow to normal in only 60%. Therefore, if one can rely on the efficiency of the aqueous-flow test, the medical treatment of wide-angle glaucoma is not always enough to "normalize" the eye. Of course, a considerably longer follow-up period will be necessary to correlate adequately the results of the aqueous-flow tests with field changes and the general clinical picture. However, these preliminary observations seem to indicate that in the future the aqueous-flow test might be a better indication of the state of wide-angle glaucoma and a better criterion for surgical intervention than tension studies have been in the past.

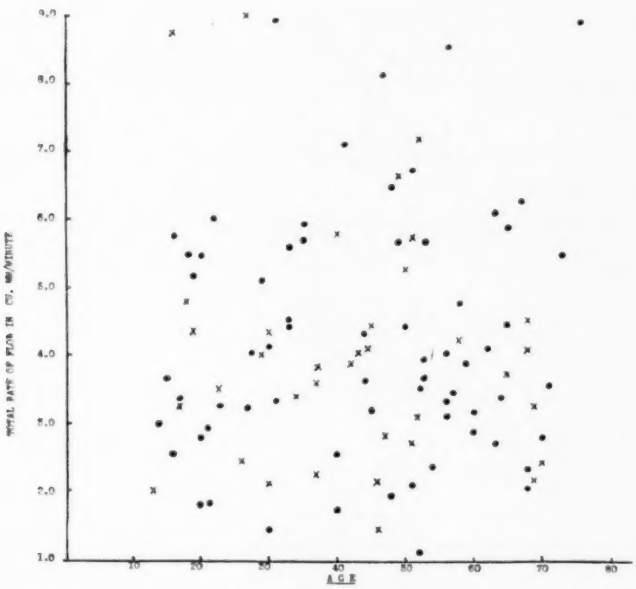

Chart 2.—Aqueous-outflow tests on 105 normal eyes, showing the relation between the total rate of flow and the age and sex of the subject.

Contrary to the promising results obtained with the wide-angle glaucomas, our results with the narrow-angle type were of less interest. When these eyes were tested during an acute rise in tension or in the congested phase, they showed a marked diminution of the facility of outflow and the net rate of flow. However, at the same time, the tension was also considerably elevated, and the diagnosis of glaucoma was obvious. When the aqueous flow was measured between these acute attacks, in the so-called quiescent stage, the values were in the normal range, and the tension was also normal. Thus, it appears that in narrow-angle glaucoma the aqueous-flow test is of only academic importance because it helps to explain the mechanism of the disease. From the practical clinical point of view, however, it did

not seem to aid us a great deal in the diagnosis. In the chronic form of this disease the aqueous flow was more variable. In spite of repeated gonioscopic examinations, it was our impression that we could not demonstrate the close correlation between the aqueous-flow test and the gonioscopic appearance of the anterior-chamber angle that Grant observed and emphasized.

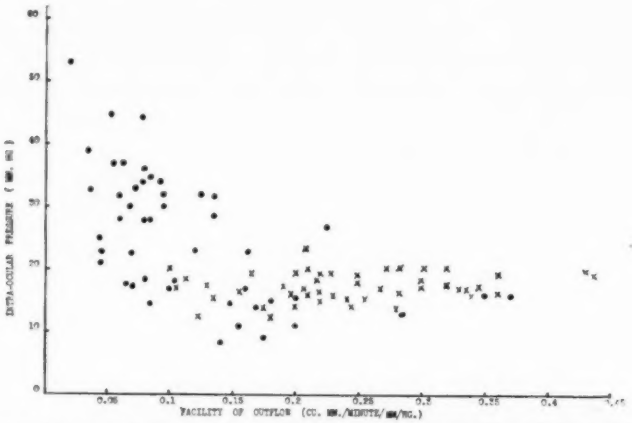

Chart 3.—Aqueous-outflow tests on 47 normal eyes, and on 47 eyes with wide-angle glaucoma that were without medication.

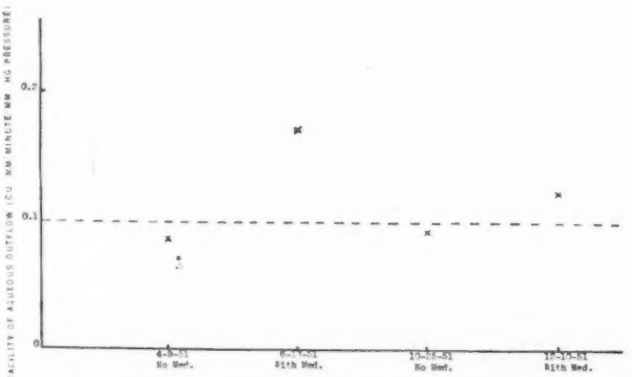

Chart 4.—Aqueous-outflow tests on the right eye of E. G., a young man with wide-angle glaucoma, showing the change in the facility of aqueous outflow following miotic medication.

The total rate of aqueous formation for all these glaucomatous eyes, both of the wide-angle and the narrow-angle type, was either in the normal range or slightly below it. At no time did the glaucoma appear to be due to an increased aqueous formation. This observation speaks against the theory of hypersecretion of the aqueous as a causative factor of glaucoma, and is in agreement with Grant's findings.

Results of our tests on glaucomatous eyes operated on indicate that the facility of outflow and the total rate of flow were within the normal range in most cases. In several instances it was noted that while the eye operated on, even without miotic medication, showed a normal aqueous outflow, the fellow (nonsurgical) eye, in spite of intensive medication, demonstrated considerably lower values. Since the follow-up period of these postoperative glaucomatous eyes has been insufficient, we do not wish to express an opinion at this time as to the usefulness of the aqueous-flow test in evaluating the results of glaucoma surgery.

Since the test was performed on only a few eyes with secondary glaucoma, pseudoglaucoma, and buphthalmos, the results obtained were statistically not significant. Therefore at this time no valid conclusions can be drawn concerning the importance of the test in those diseases.

CONCLUSIONS

The results of our studies on the aqueous-flow test, with a few exceptions, seem to substantiate Grant's thesis. In the chronic simple, wide-angle type of glaucoma it appears to be a very useful test and contributes considerably to our understanding of this disease. In the narrow-angle type of glaucoma, while it is of academic interest, it does not appear to have the same clinical importance.

We should like to emphasize that this test, at least in our hands, gave results inconsistent with the clinical evidence at hand in a small, but significant, number of cases. Therefore it should be considered only as an addition to the older diagnostic tests employed in glaucoma.

635 W. 165th St.

CONGENITAL ECTASIA OF THE CORNEA

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BOSTON

CONGENITAL ectasia and congenital staphyloma of the cornea are two rare conditions which may occur alone or may coexist with other congenital defects of the eyeball. The two terms are used rather loosely and interchangeably in the literature, and at the outset it may be prudent to define them. Ectasia of the cornea occurs as a protruding lesion, usually involving the central portion of this tissue, consisting of cornea solely and varying in degree and size; it presents a very thin, dome-like external surface, consisting largely of Descemet's membrane. A staphyloma, on the other hand, is a herniating lesion of blue-black color, which is composed not only of corneal tissue but also of iris, uvea, and, often, components of the lens, usually matted together in disorganized fashion and presenting an irregular, somewhat nodular external surface. Other congenital defects which may or may not accompany these lesions in the same or the fellow eye are microcornea, megalocornea, cornea plana, keratoconus, congenital corneal opacities of varying extent, and, in some instances, phthisis bulbi. This paper presents the clinical and pathologic findings in two cases of congenital ectasia of the cornea encountered during the past four years.

INCIDENCE

At birth a child with congenital ectasia or staphyloma of the cornea presents a bulging lesion which may occupy the greater portion of the central portion of the cornea or may involve a small central area; the greater the extent involved, the more likely is the inclusion of iris and uveal tissue to occur and the less amenable is the condition to treatment. The herniation may protrude through the palpebral fissure, or the lids may close over it in normal fashion, its extent again being the determining factor. True ectasia of the cornea, in my experience, presents an amber, extremely thin herniation surrounded by translucent and lustrous corneal tissue. Such a condition is extremely infrequent and has rarely been reported in the recent literature; the majority of cases have been recorded prior to 1920, and the first pathologic description was by Krückow,[1] in 1875. Since then a number of cases have been reported, Gallenga,[2] in 1903, collecting 13 recorded cases and reporting

Presented at the Pan-American Congress of Ophthalmology in México, D.F., Mexico, Jan. 10, 1952.

1. Krückow: Zwei Fälle von angeborenem Hornhautstaphylome: Beitrag zur Pathologie des Fötusauges, Arch. Ophth. **21**:212-235, 1875.

2. Gallenga, C.: Contributo alla conoscenza delle ectasie opache congenite della cornea da cheratite intrauterina, Arch. oftal. **11**:1-41, 1903; Delle ectasie opache congenite della cornea, Rendic A. med.-chir. de Parma **1**:58-61, 1900.

the pathologic features in 1 case. As already mentioned, however, the terminology employed was rather confusing, since in some instances the term ectasia was used when the condition was quite definitely a staphyloma. In Gallenga's article the condition was bilateral in two cases; in the remaining cases, of unilateral ectasia, the condition of the fellow eye varied from being entirely normal, in three cases, to one of microphthalmos, total corneal leukoma with vascularization, or phthisis bulbi. In other reports, namely, those of Bernheimer,[3] Coats,[4] Collins,[5] Dolbeau,[6] Lawson and Coats,[7] Nettleship,[8] and Peters,[9] the condition of the fellow eye was described as normal or was not recorded. Congenital ectasia of the cornea may exist, then, with the condition of the opposite eye varying from completely normal to one of phthisis bulbi. The condition occurred in equal numbers and frequency in both males and females.

ETIOLOGY AND PATHOLOGY

In an endeavor to arrive at the cause of the condition, the present cases are of interest not only because of the ocular changes but because investigation of them may throw light upon obscure intrauterine processes which produce various other types of neonatal pathology. Heretofore, the pathologist was obliged to reconstruct and interpret a sequence of events by examination of the enucleated specimen obtained after birth; at present, tissue is being obtained from premature infants and from fetuses which gives promise of demonstrating a more exact and a truer picture of what takes place. At present most pathologists believe that congenital ectasia and staphyloma of the cornea eventuate through transmission of an infection from mother to child *in utero*; i. e., it occurs on an inflammatory basis. A similar method of transmission has been described in congenital syphilis and toxoplasmosis. Coats,[4] in 1910, ascribed the condition to endogenous infection, transmission taking place through the placental circulation; he noted that fetal keratitis, iritis, cyclitis, and choroiditis had conclusively been demonstrated to occur endogenously but suggested that there was some difficulty in explaining how the infectious agent gained access to the cornea, since the cornea is an avascular structure and since the lesion corresponds to a perforating type of infection of exogenous origin. Heath,[10] however, was of the opinion that the method of transmission might well come about through the limbal circulation. Exogenous infection through the amniotic fluid

3. Bernheimer, S.: Total Congenital Staphyloma of the Cornea with Dermoid Formation, Arch. Ophth. **17**:417-426, 1888.

4. Coats, G.: Congenital Anterior Staphyloma, Ophthalmoscope **8**:248-257, 1910.

5. Collins, E. T.: Congenital Anterior Staphyloma, Tr. Ophth. Soc. U. Kingdom **29**:169-187, 1909. Collins, E. T., and Hudson, A. C.: A Case of Congenital Anterior Staphyloma, ibid. **33**:158-173, 1913.

6. Dolbeau: Staphylome sphérique congénital des deux carnées, Bull. Soc. chir. Paris **6**:347-349, 1865.

7. Lawson, A., and Coats, G.: Further History and Pathological Examination of a Case of Congenital Anterior Staphyloma Previously Shown by Mr. Arnold Lawson, Tr. Ophth. Soc. U. Kingdom **26**:36-43, 1906.

8. Nettleship, E.: Two Cases of Congenital Staphyloma of the Cornea, Tr. Ophth. Soc. U. Kingdom **24**:63-66, 1904.

9. Peters, A.: Zur Frage der angeborenen Staphylome, Klin. Monatsbl. Augenh. **76**:803-807, 1926.

10. Heath, D.: Personal communication to author, 1950.

might be postulated, but there are objections to this hypothesis, namely, that the eyelids are closed from the third month until shortly before birth and, second, that the newborn infant seldom shows evidence of conjunctival or ciliary congestion and inflammation, such as would be expected in the case of exogenous infection. Certainly, the absence of congestion of the eyeball was noteworthy in the two cases which I observed. The chief difficulty is that our ignorance of antenatal pathology is such that a clear explanation is not yet possible. Cases exemplifying the theory of intrauterine inflammation have been recorded by Parsons,[11] Marchesani,[12] Runte,[13] Seefelder,[14] Schiess-Gemuseus,[15] and von Hippel,[16] although the exact method of transmission was not stated in any case.

An opposite theory, that of maldevelopment or primary aberration with complete absence of evidence of inflammatory changes, together with the presence of other developmental anomalies, has been brought forward by various authors. Peters,[9] Collins,[5] Seefelder,[14] and Steinheim [17] are proponents of this view; they recorded beliefs concerning the primary aberration and cited cases to demonstrate these conditions. Steinheim recorded the incidence of a familial type in a family of six, four of whom were born with either anterior staphyloma or congenital corneal opacities. Occurrence of the condition in brothers was mentioned by Krückow [1] and Crompton,[18] while Coats stated the belief that these cases demonstrated a diseased state of the father or the mother, possibly from some disease of the uterine mucous membrane not affecting the mother but causing disease in the offspring; a familial incidence, therefore, would not necessarily indicate unrestricted hereditary transmission.

In 1904 Parsons, in a convincing article, cited 15 case records (covering about 90 years) and described the pathological examination of one case, that of an infant aged 3 days. The right eye was normal, while the left showed a complete anterior staphyloma, the lesion protruding ½ in. (1.27 cm.) beyond the lids. There was no anterior chamber, and the iris was adherent to the pseudocornea, which was very thin and almost transparent. Sections showed that the sides of the staphyloma consisted of cornea of normal thickness with the presence of Descemet's membrane, while its apex was very thin with absence of Descemet's membrane. Bowman's membrane was everywhere absent. The substantia propria was infiltrated with polymorphonuclear cells, and the staphyloma was lined with thin, disorganized iris

11. Parsons, J. H.: Congenital Anterior Staphyloma, Tr. Ophth. Soc. U. Kingdom **24**:47-63, 1904.

12. Marchesani, O.: Angeborenes Hornhautstaphylom, Ber. deutsch. ophth. Gesellsch. **48**:340, 1927; Beitrag zur Entstehungsweise der angeborenen Hornhautstaphylome, Arch. Augenh. **103**: 632-642, 1930.

13. Runte, J.: A Case of Congenital Staphyloma of the Cornea, Arch. Ophth. **36**:59-64, 1907.

14. Seefelder, R.: Pathologisch-anatomische Beiträge zur Frage der angeborenen zentralen Defektbildung der Hornhauthinterfläche, Klin. Monatsbl. Augenh. **65**:539-555, 1920.

15. Schiess-Gemuseus: Vier Fälle angeborener Anomalie des Auges: IV. Angeborenes Corneal Staphylom, Arch. Ophth. **30**:204-209, 1884.

16. von Hippel, E.: Über angeborene Hornhautstaphylome, Ber. Versamml. deutsch. ophth. Gesellsch. **46**:129-132, 354, 1927.

17. Steinheim: Zur Kenntniss der angeborenen Staphylome der Hornhaut, Centralbl. prakt. Augenh. **21**:353-358, 1897.

18. Crompton: London M. Gaz. 1840, p. 432.

tissue. The ciliary body was engorged with blood; the vitreous contained inflammatory coagulum, and the retina, choroid, and optic disk were inflamed. There was no doubt that the eye was infected, and the changes were similar to those of postnatal staphyloma following perforating ulcer of the cornea. The author, however, made no mention of the route or method of infection. In stating the opposite view, that of an anomaly, Collins expressed the belief that the initial causative aberration was a failure of differentiation of mesoderm forming the substantia propria and iris stroma, so that from the beginning the iris was united with the cornea. The bulging would occur as soon as aqeous secretion raised the tension; this is a possible explanation, and further pathologic reports substantiating both theories are recorded.

Mann [19] believed that, on the whole, the evidence points to an inflammatory origin for most cases, but she also stated:

> . . . Faulty differentiation of the mesoderm might produce the same condition; if the mesoderm failed to grow between the surface ectoderm and the optic cup in its usual three waves (1) Descemet's membrane, (2) substantia propria, (3) iris stroma and pupillary membrane—a condition of welding of the iris to the cornea might occur. It is more likely that secondary hydrophthalmia would result rather than bulging of the cornea alone.

Nevertheless, evidence that true aberration in this area may occur is the occasional incidence of corneal dermoids. Inflammation seems the more likely etiologic agent, however, the infection arriving through the amniotic fluid; whether the infecting agent reaches the amniotic fluid through the vagina, the uterine mucous membrane, or the placenta is not known; partial patency of the palpebral fissure must be postulated. A review of the conclusions of various pathologists who have examined enucleated specimens leaves one with the impression that, although there is definite evidence of an inflammatory basis for most cases, there is also very good reason for attributing some of the changes present to primary aberration. The answer will have to be found in more complete investigation of neonatal specimens in the future.

TREATMENT

Treatment of congenital ectasia of the cornea is not a simple matter, and it depends upon the extent and degree of the lesion. In cases of the prominently bulging herniations of the cornea, containing iris, lens, and uvea and presenting an irregular nodular surface, the eye obviously is useless as a visual organ, and excision of the globe is the only method of treatment. In less severe cases, in which there is ectasia of the cornea alone, various procedures may be employed, most of which have proved of little ultimate value. The use of the Van Lint conjunctival flap to cover and splint the area of ectasia; cauterization of the ectatic area, followed by the placing of a conjunctival flap; electrodesiccation of the lesion; repeated paracentesis of the anterior chamber, and excision of the staphyloma in part or *in toto* have all been tried. As far back as 1817, Beer excised a staphyloma of the cornea, uniting the margins of the gaping wound with corneal sutures. These procedures are all of doubtful value because if the original lesion is of moderate to large extent, involving the cornea, iris, or uveal tissue, the physiologic state of the resulting globe becomes even more abnormal. If, as demonstrated in Case 1 of this

19. Mann, Ida: Developmental Abnormalities of the Eye, London, Cambridge University Press, 1937, pp. 376-379.

report, the anterior-chamber angle becomes obliterated, conditions producing raised intraocular pressure will follow, the corneal scar will again distend, and buphthalmos results. If the opposite condition, namely, lowered tension, should result, gradual atrophy of the globe may eventuate, the eye oftentimes remaining chronically congested and irritable and proceeding finally to phthisis bulbi. In most cases in which the lesion is other than relatively small in size and extent, the wisest and most practical method of treatment is enucleation. In Case 2 of this report a procedure was employed which, up to the time of the last observation, gave promise of producing a useful result.

REPORT OF CASES

CASE 1.—A white girl, aged 3 days, whom I saw in July, 1947, at the Baker Memorial Hospital, had been born at full term and was a normally developed baby, the fourth child in the family. The other siblings were normal, and there was no history of maternal disease during pregnancy. Examination revealed a normal condition except for the right eye. The eyelids and adnexa of this eye were normal; there was a slight amount of white mucoid, stringy discharge in the lower fornix; with pressure over the tear sac nothing was expressed; there was very slight conjunctival congestion of the eyeball; occupying the central cornea, however, was a protruding descemetocele, about 5 mm. in diameter and of mushroom shape with a dome-like anterior surface, narrowing below to a pedicle-like structure. This lesion was of amber color, and its external cover was extremely thin, appearing as though it would burst momentarily. The remaining portions of the cornea were normal throughout, and there was no vascularization. The anterior chamber was of normal depth, and the iris was normal. Cultures of material taken from the conjunctival sac revealed no growth of any organism. As soon as arrangements could be made, a Van Lint conjunctival bridge flap was placed over the corneal lesion; the conjunctiva forming the flap was completely excised from its adjacent tissue to lessen the possibility of retraction, and the flap remained in good position for several weeks after operation. The child made an uneventful recovery from this procedure and was seen by me at intervals during the next several weeks; the cornea remained well covered by the flap. The eye became free of congestion and was of normal size during the ensuing six weeks. I did not see the patient again for eight months, at which time examination revealed the right eye to be tremendously enlarged and typically buphthalmic, with its anterior surface protruding through the eyelids. The corneal surface was entirely opaque, vascularized, and almost nodular. No view of the anterior chamber, iris, or interior eye could be obtained. The eye was firm to palpation. Because of the obvious worthlessness of the eye as a visual organ and because of its unsightly appearance, enucleation was advised and performed in March, 1948. The pathologic examination of this eye was done by Dr. Parker Heath, and his report and comment on the etiology and pathology follow:

"Pathologic examination revealed old vascular keratitis, a leukomatous scar, and staphyloma; a remnant of conjunctival flap attached to the cornea; an epithelial cyst in the corneal stroma; complete anterior synechiae and late atrophy of the iris; occlusion of the anterior-chamber angle and probable congenital angle defect; aphakia, with a few remnants of the lens; exaggerated atrophy of the ciliary body; marked atrophy of the choroid; separation of the retina; exaggerated glaucomatous cupping of the optic disk; advanced optic nerve atrophy, of glaucomatous type, and buphthalmos.

"The exaggerated degree of atrophy shown in the ciliary body, retina, and optic nerve head and nerve substance is somewhat out of proportion to the amount of atrophy to be anticipated from glaucoma alone. Evidence of primary inflammation in this specimen is substantially in the cornea and iris. It would seem that enough evidence is displayed in the angle, together with the disproportionate atrophic and buphthalmic changes, to indicate that a congenitally defective eye has been subjected to glaucoma and inflammation."

In this case is presented the sequence of events which followed the placing of a Van Lint flap over an area of corneal ectasia in an attempt to prevent bursting of the lesion and to salvage the eye for possible future keratoplasty and visual

improvement. Rupture of the ectatic lesion probably took place beneath the flap, together with closure of the anterior-chamber angle, increased intraocular pressure, and buphthalmos. The pathologist, however, stated the belief that an element of maldevelopment associated with probable primary inflammation produced the final condition.

CASE 2.—M. W., a white girl aged 5 days, was a normal, full-term baby, the first child of the parents. There had been a normal pregnancy with uncomplicated delivery, and examination revealed a well-developed infant with a normal physical condition except for the right eye. The eyelids and conjunctiva of the right eye were normal, with only slight congestion of the eyeball; the central cornea showed a protruding area, about 4 mm. in diameter, located slightly to the nasal side; it was dome-like and extremely thin. The remaining portions of the cornea were clear and nonvascularized. The anterior chamber was of normal depth, and the iris appeared normal. The fundus was not examined. The tension appeared normal to palpation. The left eye was entirely normal.

In 1909 Salzer,[20] in studies on regeneration of corneal tissue following processes which destroy tissue below the epithelium of the cornea, in the absence of infection and the prolapse of uveal tissue, stated that regeneration of the cornea will take place below the epithelium. He described swollen spindle cells with darkly staining nuclei, which he called "keratoblasts," and claimed that through multiplication by amitotic division, these cells form fibers and reconstruct clear corneal tissue; this tissue, especially in very young children, has frequently been observed and is distinguished histologically from the normal with difficulty, the absence of Bowman's membrane being the chief differentiating point. However, this sequence of events takes place only in the absence of any inflammatory process or vascularization; in the latter condition, granulation tissue is formed with the eventual appearance of scar and resulting impairment of vision.

Having the possibility of such corneal regeneration in mind, and because of the disappointing result obtained in the first case, I decided in the second case to use more radical treatment. After instillation of 5% phenylephrine (neo-synephrine®) hydrochloride to obtain maximum dilation of the pupil, a paracentesis of the anterior chamber was done, with the patient under ether anesthesia. Two loops of a 000000 surgical silk suture were placed around the pedicle of the bulging lesion, which was then held upward in a taut position, and the entire area of ectasia was excised at its base with iris scissors. This excision left a rather irregular elliptical opening in the cornea, the edges of which were brought together by placement of three 000000 surgical silk sutures through the edges of the wound and approximation of the superior and inferior lips. A certain amount of overriding tissue upon the nasal and temporal portions of the wound was excised before the end-sutures were placed. A Van Lint conjunctival flap was then brought upward from below, covering the wound, and was sutured with 00000 plain surgical gut. The patient made an uneventful convalescence from this procedure, and five days after operation the conjunctival flap had receded to some extent, and one could see that the anterior chamber had re-formed. I was able to follow this patient for five months; during this time the eye developed normally except that a dense central corneal opacity, approximately 6 mm. in length and 4 mm. in width, formed a depressed area with ridge-like edges in the central portion of the cornea and the entire cornea, as it developed, became slightly smaller than the opposite one. During May, 1950, the family moved to Wyoming; although I requested the mother to inform me as to the child's condition and referred her to an ophthalmologist there, I have no further information in regard to the case. It is my impression, however, that the procedure which was done prevented, up to the time of last observation, the occurrence of the complications encountered in the first case, namely, buphthalmos with subsequent loss of the eye. If future examination shows no evidence of increased tension, a corneal transplantation may be done to improve visual acuity.

Castroviejo[21] has performed such an operation on patients with extensive corneal opacities at the age of 2 years and on one infant at the age of 6 months,

20. Salzer, H.: Arch. Augenh. **64**:379, 1909.

21. Castroviejo, R.: Personal communication to author, 1950.

using border-to-border corneal sutures. At the time that I performed this procedure, i. e., excision of the corneal ectasia, I did it quite independently; but in reviewing the literature in preparation of this paper, I discovered that it had been done several times before—in most instances, however, in cases of corneal staphyloma, and without its being productive of a useful result.

In certain cases of true ectasia of the cornea in which the lesion is small, it would appear logical, nevertheless, to perform excision of the lesion with suture of the corneal wound; this procedure should be followed by a corneal transplantation, to be done later, in accordance with the judgment of the surgeon.

SUMMARY

Two cases of true congenital ectasia of the cornea are presented. In the first the lesion was covered with a Van Lint conjunctival bridge flap; buphthalmos ensued, with eventual loss of the eye. In the second the area of corneal ectasia was excised, and the edges of the corneal wound were sutured and covered with a receding conjunctival flap, to be followed by corneal grafting. After five months of observation this procedure appeared to be successful, and it would seem to be a worth while maneuver in such cases.

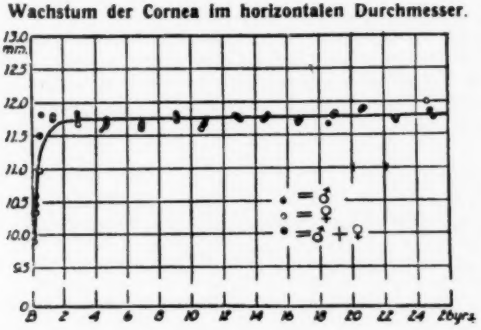
520 Commonwealth Ave.

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

EXTREME AXIAL HYPEROPIA

The case of a remarkably high degree of hyperopia is recorded. The diagnosis of glaucoma was made, but later this seemed to be disproved. Diagnostic considerations, which are important in such cases, are briefly outlined and commented upon.



Growth of the cornea, in terms of transverse diameter. From Steindorff,[1] p. 178, Fig. 1.

S. J. F., a 4-year-old white girl, was brought for examination in 1946. The mother had observed that the child had difficulty in finding small articles about the house and that she held pictures very close to her eyes.

The eyes were small. Each cornea measured 10 mm. in transverse diameter. The pupils were equal and active to light. There was low-grade alternating divergent strabismus. Ocular tension seemed normal to finger palpation. The pupils were dilated with eucatropine (euphthalmine®) hydrochloride, 5%, and phenylephrine (neo-synephrine®) hydrochloride, 2.5%. The refractive errors were +21.00 and +20.00 D. in the right and left eyes, respectively, and these lenses gave a visual acuity of 20/120 for each eye. The fundi appeared normal. The patient was seen again in 1948 and 1949. After further retinoscopy she was given corrective lenses of +17.75 sph. ⌒ +0.50 cyl., axis 90 and +17.50 sph. ⌒ +1.00 cyl., axis 110, and these lenses gave her 20/70 vision in each eye. Late in October, 1951, there was complaint of blurring of vision, and both eyes were congested. The corneas remained clear, and the pupillary responses were normal. Tension was 39 mm. in the right eye and 35 mm. in the left eye (McLean). Pilocarpine nitrate solution, 2%, was given for use four times daily in each eye. A week later the tension was 45 mm. in each eye (McLean). It was thought that the child had glaucoma and that further studies were indicated.

A summary of studies made in the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital follows:

Both eyes were small with a transverse corneal diameter of approximately 10 mm.[1] (see Chart for normal values). The anterior chambers were of normal depth. Both disks showed blurred outlines consistent with the high degree of hyperopia. Visual fields were apparently normal to 6/330 white peripherally and 9/1000 white centrally; the field examinations were made with difficulty. An attempt to examine the chamber angles gonioscopically was unsuccessful. The radius of curvature of the corneas was 6.75 mm. (normal values, 6.75 to 8.88 mm.[2]), despite the over-all hyperopic status of the eyes. The tension of both eyes was checked repeatedly during the four days. The readings were fairly consistent: Tension in both eyes was read as 3.0 with the 5.5-gm. weight and as 6.0 with the 10-gm. weight. Correction of these readings for scleral rigidity with the Friedenwald tables showed a scleral rigidity of 21 and a corrected intraocular pressure of 11 mm. Hg (Schiøtz). Dilation of the pupils with homatropine did not produce any rise of ocular tension. Aqueous-outflow studies, carried out according to the method of Grant, gave normal results. On the basis of these findings it was thought that the apparent increase in intraocular pressure was probably secondary to the abnormal size of the eyeball and to the abnormal radius of curvature of the cornea. Retinoscopy after dilation of the pupils with homatropine showed an error of +18.00 sph. ⊂ +1.00 cyl., axis 90 for each eye, and with this correction visual acuity was 20/50—1 in the right eye and 20/70 in the left eye.

Comment.—In this case the amount of hyperopia was extreme. It seemed necessary to utilize what is known regarding scleral rigidity and aqueous outflow to disprove the diagnosis of glaucoma in this case.

It is obvious that further work on the relationship of aqueous outflow, scleral rigidity, and corneal measurements is necessary. Consequently, careful observations are to be made on this patient from time to time, since the absence of glaucoma has not been established beyond question.

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Annual Reviews

PHARMACOLOGY AND TOXICOLOGY

IRVING H. LEOPOLD, M.D.
PHILADELPHIA

ANTIBIOTICS AND CHEMOTHERAPY

DURING the past year several new antibiotics have been introduced, and the literature concerning the toxicity, tolerance, penetration, and effectiveness of the older antibiotics is voluminous.[1-18] Attention has been paid in the past year to

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(Footnotes continued on next page)

the extracts of Bacillus subtilis,[1a-d] to the nitrofurazones, and to other new antibiotics.[19]

New Problems.—Several new problems have developed in the therapy of infection. There is an increase in prevalence of infection due to strains resistant to the available antibiotics.[2-18] There is also the unsolved problem of infections developing

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(Footnotes continued on next page)

Penicillin.—New forms of penicillin are constantly being developed.[20] "Compenamine" is a penicillin salt of N-methyl-1, 2-diphenyl-2-hydroxyethylamine. This base is thought to possess certain antiallergic properties which apparently are not

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related to any antihistaminic action. N-N'dibenzylethylenediamine penicillin ("bicillin") or DBED penicillin is an insoluble salt of penicillin recently synthesized, and it can be administered orally. The inclusion of procaine in the penicillin molecule produces a repository form of the drug.[21] Several of these penicillins have been

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(Footnotes continued on next page)

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Antifungous Substances.—The ability of various micro-organisms to produce chemical substances that have a pronounced inhibitory effect upon the growth of fungi now has been established.[1x] Some of these substances, such as actidione, antimycin, fradicin and fungicidin, are active only on fungi, and not at all, or to

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a very slight degree, on bacteria and actinomycetes. Others, like actinomycin, gliotoxin, clavacin, and streptothricin, are active against both bacteria and fungi. Most of the important antibiotics, such as penicillin, aureomycin, terramycin, neomycin, streptomycin, and chloramphenicol, are not active against true fungi.

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(Footnotes continued on next page)

Newer Antibiotics.—From the data available during the past year,[1-18] the tables that were prepared for last year's review appear to be adequate.[3f]

A wide variety of ocular diseases have responded to aureomycin,[4] chloramphenicol,[5] terramycin,[6] polymyxin,[7] neomycin,[8] and sulfonamides.[9]

Polymyxin [7] has been found effective against Pseudomonas aeruginosa. However, both polymyxin B and polymyxin E produce nephrotoxicity when used systemically. This effect usually disappears if treatment is not employed over four to seven days. Neurotoxicity also occurs, expressed usually as hyperesthesia or paresthesia about the mouth and face, and occasionally as nystagmus.

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19. Micks, Whitney, and Anigstein.[1e] Davisson and others.[1f] Wachter and others.[1g] Kenner and Murray.[1h] McCowen, Callender, and Lawlis.[1v] Raubitscheck, Acker, and Waksman.[1w]

20. Elias, Price, and Merrianon.[2e] Longacre.[2f] Siegal.[2g] Adair, Woodin, and Bunn.[2l] Epstein and Allen.[2m] Kadison, Ishihara, and Waters.[2r]

21. Longacre.[2f] Jensen and others.[2t]

The problem of the oral administration of bacitracin [3] is just beginning to be explored. Only small quantities are absorbed when the drug is administered orally. It has the same antibacterial spectrum as penicillin but also is active against some penicillin-insensitive strains. It works well in combination with penicillin and with neomycin.

Neomycin [8] continues to be found effective against Gram-negative organisms, the tubercle bacilli, Treponema and Endamoeba histolytica, but is only weakly effective against some Gram-positive organisms and Clostridia. It possesses nephrotoxicity and neurotoxicity. The toxic effects of neomycin and streptomycin are additive. Neomycin has been effective in dermatologic infections, as well as in many forms of tuberculosis. Chloramphenicol may produce aplastic anemia.

Influence of Antibiotics on the Community.—More than a decade has passed since the first patients were successfully treated with penicillin. In this decade somewhat of a revolution has occurred in medicine. We are now in what may later be termed the "antibiotic age." More than 300 antibiotic substances have been discovered, but perhaps only 5 can be considered as having reached major status. These five are penicillin,[2] streptomycin or dihydrostreptomycin,[3] aureomycin,[4] terramycin,[6] and chloramphenicol.[5] Others which are of considerable importance but have not quite reached their majority in widespread usefulness are polymyxin,[7] bacitracin,[3] and neomycin,[8] and perhaps we should also include in this group agents such as tyrothricin [1j] and viomycin.[17e,f-h] The other antibiotics have fallen short, for several reasons. They may be too toxic; they may be not very effective in vitro. No one knows how many investigators are engaged in the search for new antibiotics or exactly how many laboratories and hospitals are carrying on these studies. The literature of reported work is already enormous. It has been estimated that no fewer than 18,000 research papers on antibiotics have been published since 1940. The bibliography on the three-year-old drug aureomycin, alone, lists more than 3,000 titles, and the literature on penicillin and streptomycin is much larger. As is pointed out by Raper [1r] antibiotic research has fostered considerable teamwork. Scientists have been brought together on vast scales, from many different fields, such as mycology, physical chemistry, clinical medicine, chemistry, and engineering.

It may not be far afield to mention what extremely "big business" antibiotics constitute today. The penicillin production in 1951 of some 350,000,000,000,000 units was worth about $140,000,000, even at the wholesale value of 40 cents per 1,000,000 units. On the same basis, the streptomycin production of more than 150,000,000 gm. last year at 38 cents a gram wholesale, was worth nearly $57,000,000. The sale of other antibiotics amounted to about $90,000,000 in 1950, the latest year for which an estimate is available, and we can be sure it was greater in 1951. It is also interesting that antibiotics represent an increasingly important part of drug store prescription business. They accounted for approximately 25% of all prescriptions filled in 1950, and antibiotics are well in the lead over all other prescription products.

Bacterial Resistance.—Many investigators continue to study the problem of bacterial resistance.[10] Most authors have demonstrated that the penicillin-resistant staphylococci produce a penicillinase and that none of the sensitive strains produce this penicillinase. It was also noticed by Chandler and his co-workers [10i] that exposure of the penicillinase-producing Staphylococcus to aureomycin produced a loss in the capacity of that organism to produce penicillinase and that this loss appeared to be irreversible. The clinical implications of these observations are that when, in the course of an infection that is being treated with penicillin, the infecting organism is discovered to be one that produces penicillinase, the substitution of another antibiotic to which the organism is sensitive not only is indicated but may at some later date allow the reintroduction of penicillin if the organism loses its capacity to produce penicillinase. In the case of staphylococcic infections,

the substitution of aureomycin for penicillin would seem to constitute a logical procedure, in the light of observations made by Chandler and his group.

A cross resistance between streptomycin and neomycin has been demonstrated; that is, organisms which have developed a resistance to streptomycin may be resistant to neomycin, and the reverse may also be true. However, no cross resistance could be demonstrated between organisms resistant to neomycin and streptomycin and the chloramphenicol-aureomycin-terramycin group. Organisms found to be resistant to the chloramphenicol-aureomycin-terramycin group were not resistant to polymyxin D. Cross resistance may exist, even though the bacterium has not formerly encountered the second antibiotic. For example, an organism which has developed a resistance to streptomycin may be resistant to neomycin even though it has never encountered neomycin.

Such observations may indicate some of the methods by which the antibiotics operate. For example, if the antimicrobial action of antibiotics is due to the interference with one or more of the bacterial enzyme systems, then those agents which show cross resistance may exert their action along common pathways. In addition, evidence has been presented which indicates that a cross resistance to antibiotics may develop during therapy. We can no longer hold the idea that the increased microbial resistance that frequently follows exposure to antibiotics is a characteristic of the antibiotic itself, and that the organism would probably not show increased resistance to other antibiotics, for it has repeatedly been shown in the literature that acquired resistance to terramycin was often accompanied by a decreased sensitivity to aureomycin and that acquired resistance to aureomycin or chloramphenicol was accompanied by cross resistance to the other agent and to terramycin. Organisms that developed a resistance to aureomycin, chloramphenicol, or terramycin showed in general a simultaneous increased resistance to the other two antibiotics. Cross resistance between aureomycin and terramycin was most commonly encountered, but there was no indication of cross resistance between aureomycin, chloramphenicol, and terramycin, on the one hand, and of dihydrostreptomycin, on the other. In fact, organisms resistant to one of the broad-spectrum antibiotics often seemed to have acquired increased sensitivity to streptomycin, and vice versa.

Superinfection.—The term "superinfection" has come into use to describe fresh complicating infections arising during antibiotic therapy. Usually one sees an initially favorable response to treatment, followed by a worsening of the patient's condition, associated with the appearance of bacteria resistant to the drug, which had not been noted before. Antibiotics administered systemically suppress bacterial flora in many parts of the body not involved at the time of beginning of therapy. Penicillin, particularly, suppresses the bacterial flora in the mouth, owing to its presence in the saliva. After large amounts of penicillin, choliform bacilli appear in the mouth. Other antibiotics produce the same effect elsewhere in the alimentary tract. Aureomycin may suppress intestinal flora, and if treatment is continued, the intestinal flora may be replaced by Pseudomonas, yeast, and staphylococci resistant to drugs. Candida albicans is highly resistant to chemotherapeutic agents. Abbott and his co-workers [10m] describe a case of bronchopneumonia in which the patient succumbed after massive doses of antibiotics, namely, penicillin, streptomycin, and chloramphenicol. In the sputum of this patient, C. albicans organisms were

abundant, and at autopsy cavitating pulmonary aspergillosis was discovered. It is possible that the antibiotics were responsible for the fungal infections and death. These antibiotics may suppress normal bacterial flora and thus upset a balance that is holding fungal growth in check. On the other hand, there is evidence that antibiotics may stimulate active growth of the fungi.[10o] Pappenfort and Schnall [10p] report C. albicans infections in 16 patients treated with aureomycin; they found that this drug stimulated the growth of the C. albicans in vitro. However, they thought that this action might be due to an impurity in the preparation, and not to the aureomycin itself. It is important to realize that there are many fungi that will not respond to chemotherapeutic and antibiotic therapy. We must be on our guard and prepared to diagnose the ocular, as well as the systemic, manifestations of these organisms, for in these days of widespread use of antibiotics such fungal superinfections are going to occur. For this reason, particular attention should be paid to the recent review of ocular manifestations of fungal involvement and their therapy

TABLE 1.—*Treatment of Mycotic Infections*

Leptothricosis conjunctivitis.....	Excision of gray area in the conjunctiva with biopsy; penicillin given parenterally to check lymphadenitis
Monilinsis	General supportive measures, e. g., rest, vitamins; iodides, ascending doses; x-rays to superficial areas; eradication of all foci
Actinomycosis; streptotrichosis..	Early excision of local lesion if possible; iodides; x-ray therapy; thymol, 1:1,000 aqueous solution, for local lesions; sulfonamides, penicillin, aureomycin, and streptomycin of possible value
Sporotrichosis	Iodides; surgery contraindicated; x-rays of possible assistance in the blocking of lymph channels; penicillin and sulfonamides of no value
Blastomycosis	Surgical excision of small local lesion; x-ray therapy; iodides; desensitization and antisera helpful
Cryptococcosis (torulosis).....	Iodides; penicillin; sulfonamides
Aspergillosis	Iodides; supportive treatment
Coccidiodomycosis	Supportive treatment; chloramphenicol
Histoplasmosis	Organic antimony salts (stibophen U. S. P. or stibamine glueoside)

by Birge.[3h] Therapy of these conditions is not satisfactory. What is known has been summarized in table 1, modified from information supplied by Birge.[3h]

It is difficult to account for the mechanism of resistance development. It could be due to mutation of the organism, or perhaps to a change in internal metabolism, so that the type of metabolism which is blocked by the antibiotic to which the organism develops resistance is altered. The organism now uses a second route of metabolism, so that the antibiotic can no longer interfere with its metabolic processes. There is a possibility that the organism forms an antibiotic ase, that is, something like penicillinase, or that the bacterium changes its cell-membrane characteristics, so that the antibiotic is no longer able to penetrate its cell membrane. This may explain the ability of some organisms which may have been unaffected by terramycin, aureomycin, or chloramphenicol to become susceptible to these agents if the organism is allowed to remain in contact with neomycin or streptomycin for a definite length of time.[10i,j]

Antibiotic Combinations.—In the 1951 review [3f] it was pointed out that the combinations of antibiotic agents have four possible effects: (1) They may interfere with the action of one another; (2) they may be additive in their effect (that is, as though one used equal quantities of two different agents, instead of a double quantity of one agent); (3) they may be synergistic, so that they produce not only

the effect of equal quantities of the various agents, but an additional effect as well (that is, the combination is better than either agent alone in equal quantity), or (4) they may have no effect. One hopes by combining antibiotics to reduce the toxic manifestations of the single drug, to reduce the possibilities of strains acquiring resistance to either drug, and to broaden the antibacterial spectrum.[11] Studies by Bliss and his co-workers [11e] suggest that the effects of combinations of antibiotics vary with the methods of testing, with the test organism, and, most important, with the concentration of the two components. The greater the concentration of the agents, the less the benefit derived from combining them. Synergism was demonstrated more frequently than antagonism among various combinations studied, but most of the reactions fell between these extremes. The effect of most combinations either was additive or did not differ from that of the agents when used separately. Synergistic combinations were those of penicillin and streptomycin, of aureomycin and terramycin, or of terramycin and chloramphenicol. Chloramphenicol has repeatedly been found to be antagonistic to penicillin and to streptomycin by both in vitro and in vivo testing. Aureomycin and terramycin were also shown by some tests to be antagonistic to penicillin and streptomycin. The mechanism of this interference, when it does occur, is not known. It is not simply substrate competition, because the chemical structures of most of these compounds are dissimilar. It is not due solely to prevention of cell division. Chloramphenicol, for example, has been found to interfere with effectiveness of penicillin, even when it is applied after penicillin has been allowed to act for a considerable length of time. In other words, the antagonism is not explained by the fact that chloramphenicol inhibits the rapid multiplication of organisms, and thus does not allow penicillin to act on rapidly multiplying organisms. However, there are other investigators who believe that the time of administration of the two agents is important in determining antagonistic and synergistic actions. For example, it is indicated by Gunnison and his co-workers [11d] that if penicillin is given a few minutes prior to the other drug, and if an excessive dose has been used, no interference can be demonstrated. The time relationship necessary for the demonstration of these effects varies with different drugs. Chloramphenicol was found to interfere with the action of penicillin if given simultaneously with the penicillin, or one or two hours prior to the administration of penicillin. Sulfadiazine, on the other hand, had no effect if given simultaneously or if given one or two hours before the penicillin, but was effective only if it preceded the administration of penicillin by at least four to six hours. From their studies, it would appear that any agent that would interfere with the multiplication rate of the organisms might interfere with the action of penicillin. It is evident, therefore, that the subject of antibiotic combinations still requires considerable study. The ideal synergistic combination, according to Miles and his co-workers,[11a] would be one in which the combination is better than either agent alone, in which one compound kills the organisms that are resistant to the other, in which one component acts on multiplying bacteria and the other on the resting organisms, in which one may potentiate the action of the other by increasing permeability of the cell wall, or in which one may block one enzymatic pathway and the other another essential enzymatic pathway in the metabolism of the organism. Most of the synergism has occurred when the antibiotics have acted simultaneously, and not in sequence; and this would favor the hypothesis of synergism involving simultaneous blocking of alternate enzymatic pathways.

There is evidence of successful therapy with combinations of penicillin and bacitracin [11j]; of streptomycin and aureomycin in brucellosis; of paraaminosalicylic acid and streptomycin, or dihydrostreptomycin, in tuberculosis,[17] and of penicillin and streptomycin, of penicillin and a sulfonamide, of streptomycin and a sulfonamide, and of bacitracin and polymyxin.[11] When in doubt concerning the value of a combination, the ophthalmologist should rely on individual agents which he knows may be effective against the responsible etiologic organism.

Drugs Employed in Chemotherapy of Tuberculosis.[17]—Sulfonamides [17j']: The sulfonamides are capable, under specified conditions, of exerting a limited, but definite, retarding effect on experimental tuberculosis. They have not been given much clinical trial, but most of the beneficial effects can probably be attributed to control of secondary infection.

Sulfones [17j']: Examples of the sulfones are diaminodiphenylsulfone, propimine diazone, and thiazolsulfone (promizole®). The sulfones are effective but are hemolytic in large doses.

Sulfetrones [17j']: Sulfetrones are mainly bacteriostatic. In combination with other drugs, they appear to be more useful than when employed alone. Several toxic effects, such as nausea, vomiting, anorexia, headache, depression, drug rash, and visual disturbance, have been reported to follow their use, and many of the patients who have been treated with sulfetrones have required blood transfusions.

Thiosemicarbazones ("Tibione"; TB1 = 698)[22]: There is evidence that this agent exerts a favorable influence on the hypersensitivity forms of tuberculosis. Perhaps it is able to detoxify the tuberculous products. There is evidence of a definite reaction between tuberculin and thiosemicarbazone. Usually one starts with a dose of 12 to 25 mg. daily, increasing it gradually until 200 mg. has been reached. It is probably safer, however, not to exceed 100 mg. daily. In the patients treated to date prolonged therapy has been necessary, the average period being approximately six months. The toxicity of thiosemicarbazone is greater than that of streptomycin and less than that of the sulfones. One sees anorexia, granulocytosis, and allergic reactions. The sedimentation rate is also affected; so it cannot be used as a guide for therapy of these patients. Thiosemicarbazones are not inhibited by streptomycin.

Paraaminosalicylic acid is usually given in dosages of 12 gm. daily; the doses are divided so that about 3 gm. is given four times a day.[23] This drug may be given by intravenous injection or orally as tablets or powders. The taste is rather unpleasant, and there is evidence that paraaminosalicylic acid delays the development of resistance of the tubercle organism. Nausea, vomiting, and malaise are some of the toxic signs.

Enzymes: Streptokinase and streptodornase (desoxyribonuclease) have been employed for complications of pulmonary tuberculosis because of their ability to lyse fibrin. They are discussed in a later section of this review. Lepri [17y] showed that the introduction of hyaluronidase into the anterior chamber after experimental tuberculous inoculation of the anterior segment of the rabbit eye increases the diffusion of the infection. Simultaneous administration of rutin, however, seems to counteract the effect of hyaluronidase.

BCG and Other Vaccines [17v', w']: There is still question as to the value of BCG and other vaccines in the development of immunity in tuberculosis.

Antibiotics [24]: Almost all the antibiotics have been tried in treatment of tuberculosis—streptomycin, neomycin, terramycin, aureomycin, mycomycin, viomycin, and chloramphenicol.

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22. Grunberg and Leiwant.[17c] Hoggarth and Martin.[17e] Wegner and Lintz.[17z] Gandolfi Morpurgo.[17a'] Belgorou and others.[17b'] Volini, Kadison, and Felsenfeld.[17c'] Marsh.[17j'] Gross and Haase.[17q'] Bunn and Drobec.[17r']

23. Gurta.[17a] Cruickshank and Mitchell.[17d] Steel.[17h] Hughes and others.[17v] Adair, Drobeck, and Bunn.[17x] Lepri.[17y] Wegner and Lintz.[17z] Volini, Kadison, and Felsenfeld.[17c'] Warring and Howlett.[17i'] Marsh.[17j'] Gross and Haase.[17q'] Bunn and Drobeck.[17r'] Mendenhall and Shaw.[17s'] Horne and MacAskill.[17u'] Pitts and Tempel.[17a''] Editorial.[17c''] Shane and others.[17d'']

24. Lepri and Capalbi.[6u] Gurta.[17a] Duca, Rothlauf, and Saidi.[17b] Oatway and Reding.[17i] Sykowski.[17u] Hughes and others.[17v] Glorig.[17w] Adair, Drobeck, and Bunn.[17x] Wegner and Lintz.[17z] Volini, Kadison, and Felsenfeld.[17c'] O'Connor, Christie, and Howlett.[17d'] Bartz.[17e'] Finley.[17e'] Ehrlich.[17g'] Harvey.[17h'] Marsh.[17j']

Of these, neither aureomycin nor chloramphenicol has been shown to have any value in tuberculosis. Terramycin may be slightly helpful. Neomycin also has some benefit, particularly if its systemic toxicity can be reduced. Mycomycin, which was isolated by Johnson and Burden in 1947, is stable only at very low temperatures, and therefore its usefulness is limited. Viomycin, although effective against tuberculosis, produces renal irritation and vestibular dysfunction, and the organism can develop resistance to this antibiotic. The present trend in the antibiotic therapy is to use paraaminosalicylic acid daily (10 to 12 gm.) and streptomycin intermittently, 1 or 0.5 gm. every other day or twice weekly.[25]

Other Drugs: Cepharanthine is reported by Hasegawa [17f] as being beneficial in tuberculosis. The dose employed was 0.1 mg. daily, and beneficial results are reported. However, poor results are reported by Ebina and co-workers.[17g] The latter workers employed 0.01 to 0.05 mg. every other day, or daily, for six months, without any beneficial effect.

Probenecid (benemid ®) has been employed to raise the level of paraminosalicylic acid, by preventing the rapid excretion of paraaminosalicylic acid. Therefore, one can use smaller doses of paraaminosalicylic acid and obtain a greater effect over a longer period.

Cortisone and corticotropin may be of some value in an effort to reduce the sensitivity to the tuberculoprotein and in cutting down the inflammatory reaction. However, it has been well shown that cortisone must be used with extreme care, as it may predispose to greater spread of the tubercle bacilli. However, it is conceivable that, if used properly, cortisone, because of its action on granulation tissue, could be administered along with an antibiotic, such as streptomycin, thus allowing the drug to attack the bacilli more readily, rather than allowing the bacilli to become encased by granulation tissue and thus become inaccessible. This procedure is a very dangerous one, however, and at present cannot be recommended.[26]

Antihistaminics [17j'] have been employed in an effort to reduce the exudative phase, which possibly may in some way be due to the release of histamine.

Cryogenine,[17j'] a phenylsemicarbazide, has been used for its antipyretic effect, but has been shown to produce hemolytic anemia.

Tuberculin is employed in an effort to reduce the hypersensitivity to tuberculin, and sodium citrate has been used because streptomycin has been shown to be more effective in an alkaline medium. Nitrogen mustards (methyl-*bis*[2-chloroethyl[amine or methyl-*tris*[2-chloroethyl] amine) have been employed in an effort to reduce exudates and to stimulate the reticuloendothelial system. The dose employed is 0.05 to 0.2 mg. per kilogram of body weight, three to five injections a week being given.

The popular press has recently given widespread publicity to a series of antituberculosis drugs, the hydrazine derivatives of isonicotinic acid.[17k-t] This premature announcement has apparently raised the hope of many patients, perhaps unjustifiably. These drugs are potent against tubercle bacilli in the test tube, in the experimental animal, and in preliminary tests in man, but no formal statement can be made as to the optimum dosage schedule, the permanence of the early results, and the possibility of development of drug resistance. The most active compound against tuberculosis in this group of thiosemicarbazones and related substances was isonicotinic acid hydrazide. It has been given the trade name of "rimifon" by Hoffmann-LaRoche, Inc., and of "nydrazid" by E. R. Squibb & Sons. This compound seems to be bactericidal. The protective and therapeutic value of the hydrazides of isonicotinic acid has been demonstrated in a variety of species, including the mouse, guinea pig, rabbit, and monkey. Daily oral doses of 2 to 4 mg. per kilogram of body weight of isonicotinic acid hydrazide or of 2 to 10 mg. per kilogram of body weight of the isopropyl derivative of isonicotinic acid hydrazide are prescribed. The toxic effects of these agents consist in stimulation of the central nervous system—symptoms suggesting modification of autonomic activity, such as dryness of the mouth, bladder-sphincter disturbances, and constipation. Dizziness, presumably due to transitory moderate decreases of blood pressure, has been encountered. There is some suggestion of renal and hepatic damage. The drug is rapidly absorbed after oral administration. Appreciable concentrations are present in the spinal fluid within three hours after an oral dose of 2 to 3 mg. per kilogram of weight in patients without meningitis, and in patients with tuberculous meningitis the concentration is substantially higher in the spinal fluid than that necessary to

25. Hughes and others.[17v] Mendenhall and Shaw.[17w'] James and others.[17t']

26. Marsh.[17j'] Woods, Wood, and Naquin.[17j''] Woods and Wood.[17k'']

inhibit Mycobacterium tuberculosis in vitro. It is extremely interesting that these agents do not show any activity in vivo against the hemolytic streptococci, Diplococcus pneumoniae, Salmonella, trypanosomes, Trichomonas, or the influenza virus. It is evident that this group of compounds has several advantages over other antituberculosis agents. Whether their use will become a definite form of therapy or whether they will be simply adjuvants will be determined by future investigation.

Ophthalmia Neonatorum.[12]—The net results to date of studies of committees and investigators in various obstetrical clinics indicate that penicillin or aureomycin prophylaxis administered under proper control is the equal of, and in some respects superior to, the established silver-nitrate procedure. Terramycin has not been as efficacious. Nevertheless, no radical change in existing laws or regulations requiring silver-nitrate prophylaxis should be recommended at this time.

The opponents of silver-nitrate prophylaxis and the proponents of the penicillin method argue that in 50% of the infants treated with silver-nitrate chemical conjunctivitis later develops, which, while not serious, is disturbing. The stock solution of silver nitrate may evaporate to the extent that the solution used is dangerously strong and may actually cause organic damage to the cornea. Occasionally mistakes, such as the use of a 10% solution instead of the proper 1% solution, have been made, and, as the result, the infant so treated is permanently blind. Penicillin is as efficacious as silver-nitrate in the prevention of ophthalmia neonatorum and carries with it none of the objections mentioned. It is argued that the net value of the silver-nitrate procedure lies in the preliminary cleansing of the eye. Those opposing the abandoning of the silver-nitrate prophylaxis at present argue that 1% silver nitrate solution does cause chemical conjunctivitis in hypersensitive infants but that such conjunctivitis is trivial; and in hundreds of thousands of cases in which it has been used there is no record that properly performed Credé prophylaxis has done any harm to the infant's eye. It has been proved to be an effective prophylactic method, and the danger of evaporation can be eliminated by the use of modern wax ampules. No possible change of laws or regulations can save an ignorant or careless physician from the results of his folly. Penicillin prophylaxis requires that the ointments or solutions be kept on ice. Even then they may deteriorate. There is also the possibility of sensitization to penicillin. It is possible that an antibiotic may be discovered which will be more efficacious against the virus, as well as the Gonococcus; therefore, the time is not ripe for a recommendation of change in the existing laws and regulations.

Herpes Simplex and Herpes Zoster.—Experimental studies have failed to reveal a single antibiotic or chemical agent that is efficacious in controlling established herpes simplex keratitis, although a number of agents appear to have some prophylactic or inhibiting action on the development of the lesion.[27] Herpes zoster has been said to respond to many therapeutic agents, including aureomycin and chloramphenicol; but recent studies in large series in which the clinical data have been fairly well controlled reveal no particular merit of either aureomycin or chloramphenicol in treatment of herpes zoster ophthalmicus or other forms of herpes zoster except for their possible benefit in control of secondary infection.[28] Antibiotics were also found to be of little value in the control of Newcastle virus conjunctivitis.[13f]

Trachoma.[14]—Thygeson [14i] and Siniscal,[14j] as well as others, reemphasize the value of sulfonamides locally and orally administered in trachoma.

Thygeson [14i] believes that sulfonamides act by interfering with the intracellular development of the virus rather than by any direct virucidal action. Many antibiotics have been tried in

27. Geller and Thygeson.[13a] Ciotola.[13e] Hallett and others.[13i]

28. Benedek.[13d] Voisin and others.[13g] Schaeffer and Svendsen.[13h] Bubbage.[13j] Kass, Aycock, and Finland.[13k] Carter. [13l]

trachoma, with reported success. Most of the evidence would indicate that their efficacy is due to the control of secondary infection.[14] Thygeson [14i] also states that the virus responsible for inclusion body conjunctivitis responds to penicillin, as does the virus of lymphogranuloma. The mechanism of action here is virustatic rather than virucidal. Penicillin and streptomycin are ineffective, but aureomycin, chloramphenicol, and terramycin are active against lymphogranuloma venereum. It has been shown that the viruses responsible for trachoma, psittacosis, and lymphogranuloma venereum, belonging to the group Chlamydozoaceae, all respond to oral and local administration of sulfonamides. This group of viruses occupies a position intermediate between the typical large viruses and the Rickettsiaceae.

Toxoplasmosis.—Straub [15a] and, more recently, Wilder [15b] have called the attention of ophthalmologists to the increasing incidence of ocular toxoplasmosis and the possibility of development of ocular conditions due to toxoplasmosis in adults.[15a] Others have shown that sulfonamides and "endochin" (3-hyptyl-7-methoxy-2-methyl-4-quinolinol) an antimalarial drug, have delaying effects upon the course of this disease. Sulfadiazine appeared to be somewhat superior to "endochin," and the combination was not more successful than sulfadiazine alone.[15c] Kass and Steen [15d] have found aureomycin to have a favorable influence on acute experimental toxoplasmosis in rabbits.

Dosage Schedules.—Although the literature concerning antibiotics has been voluminous again this year, there is no reason to change the schedules from those suggested in the 1951 review. The toxicity of antibiotics also appears very much the same.[1-18] The new antibiotics have been found to show practically the same types of toxicity as do the older ones.[29]

Selection of Antibiotic.—Again, the tables prepared for the 1951 review as a general guide to organisms sensitive to antibiotics may still be used. Additional evidence has been brought forth in the past year confirming the value of salts of propionic acid.[30] In addition, attention has been called to the value of the nitrofurazone (furacin®) derivatives in ophthalmology.[1y] It is still necessary to know the ability of each antibiotic to penetrate the blood-aqueous barrier when systemically administered and its local penetrating ability. Studies have been carried out by many investigators concerning terramycin, chloramphenicol, and other antibiotics.[31] It has been confirmed by all these investigators that terramycin penetrates extremely poorly into the intact globe, and that penetration is somewhat increased, but not strikingly so, by removal of the corneal epithelium preceding local application. Systemically administered terramycin penetrates poorly into the normal eye. Langham [16b] has confirmed earlier studies of Leopold, Nichols, and Vogel [16c,d] showing the greater ability of chloramphenicol than of other antibiotics to penetrate from the

29. Wilson, Deeds, and Rather.[1a] Sacks.[1b] Kaiser.[1c] Quinn.[1d] Micks, Whitney, and Anigstein.[1e] Davisson and others.[1f] Wachter, Bohonos and Quakenbusch.[1g] Kenner and Murray.[1h] Berger and others.[1i] Dimick.[1j] Takano.[1y] Dubois-Poulsen, Dubois-Verlière, and Tibi.[1z] Siegal[2g] Harkavy.[2j] Spring.[2k] Adair, Woodin, and Bunn.[2l] Kmonicek.[3c] Payne, Spencer, and Schultz.[3d] Eggers.[3e] Reiches.[4h] Ayre.[4i] McVay and Sprunt.[4m] Mercier.[4r] Usadek, Curtis, and Mill.[5d] Berens and Gulyash.[5h] van Gelderen.[5k] Roberts.[5n] Willcox.[6s] Cannon, Nichols, and Leopold.[6w] Douvas, Featherstone, and Braly.[6x] Brownlee, Bushby, and Short.[7d] Hambre and others.[8n] Vogel, Leopold, and Nichols.[8f] Hagerman and Franzblau.[9c] Cruickshank and Mitchell.[17d] Steel.[17h] Editorial.[17k] Selikoff, Robitzek, and Ornstein.[17s] O'Connor, Christie, and Howlett.[17d'] Warring and Howlett.[17l']

30. Dubois-Poulsen, Dubois-Verlière, and Tibi.[1z] Melodia.[1a']

31. Lepri and Sicca.[6v] Cannon, Nichols, and Leopold.[6w] Douvas.[6x] Frisk and Tunevall.[6q]

blood stream into the eye. Langham suggests that it is the relative affinity of these antibiotic compounds for the lipids of the cell membranes that determines their rate of entity.

Substances which are strongly soluble in water, such as sugars and amino acids, have a partition coefficient so low that for practical purposes they may be considered completely lipid-insoluble, and they enter through intercellular spaces. The main evidence for this is the observation that the rate of entry is in inverse proportion to the size of the particle. This is indicated by the fact that sucrose, having a molecular weight of 342, passes into the anterior chamber, whereas raffinose, having a molecular weight of 504, does not. In contrast, in the case of lipid-soluble compounds, the evidence presented by Langham indicates that size can be of only secondary importance, the rate of entry being proportional to the lipid solubility of the compound. Streptomycin is a lipid-insoluble compound. Therefore, its entry will depend on its molecular size. Particles which enter by way of the cellular spaces by simple diffusion should have a molecular weight below 500. Streptomycin has a molecular weight of 743, and therefore it should not be expected to pass the barrier. Aureomycin and polymyxin also are compounds of a lipid-insoluble nature and would not be expected to pass the barrier rapidly. Thus it becomes apparent that the lipid-soluble substance may enter through all the barriers found in the aqueous humor. Of the antibiotics in common clinical use, chloramphenicol passes most readily into the intraocular fluids from the blood stream; so for intraocular infections this drug must be given serious consideration.

The problems of antibiotic therapy have been multipled by the increase in number of commercially available antibiotics and the number of bacterial strains resistant to one or more of them.[18] Selection of the most effective antibiotic for treatment of a certain infection is frequently difficult. The clinician, in his selection of an antibiotic for treatment of an infection of uncertain bacterial origin, has several possibilities. He may assume, from the clinical appearance, the possible etiologic organism. Often this method is successful, but frequently the first drug tried is ineffective because of lack of susceptibility of the infecting agent. Valuable time may be lost in blind clinical trial. Bacteriological analysis may identify the organism, allowing him to pick the agent likely to succeed on the basis of previous experience; but, because of the possibility of one strain not being the same as other strains of the same organism in its response to antibiotics, this method may fail. Therefore, some investigators may try to find the organism and determine its in vitro sensitivity to the available antibiotics. Theoretically, the latter method is the best, but there are objections to this. Clinical results do not always parallel the results of laboratory tests with antibiotics. Various sensitivity tests in the laboratory are not as accurate as many clinicians believe, for the results of such tests will vary with the size of the inoculum, the period of incubation, and the factors which are used for the end-point, that is, the means by which one determines whether it is complete or partial inhibition which is significant. A difference in media may make a difference in the results. The size of the inhibition zone does not definitely indicate the effectiveness of the antibiotic used, for the size of the inhibition zone may depend upon the ability of the antibiotic to diffuse through the medium used for in vitro testing. It is apparent that there are many pitfalls in the application of sensitivity tests to the clinical control of antibiotic therapy. Further refinements of technique and correlation of clinical and laboratory results are necessary. Spaulding and Anderson [18p] suggest that sensitivity tests be performed in all cases of fulminating infections, in cases of infections not responding after 72 hours of antibiotic therapy, and in cases in which relapses occur during therapy or in which there are evidences of changes in the bacterial flora.

Marshall [18g] points out that the dosage schedules employed and suggested for chemotherapeutic and antibiotic agents require review. There is considerable question whether penicillin should be given at regular intervals and in sufficient concentration to maintain a constant antibacterial level in the blood stream. Marshall has accumulated evidence suggesting that penicillin is equally effective when given intermittently and when intervals of very low levels of antibacterial action have been evident in the blood stream.

The situation in regard to the dosage schedule of streptomycin in bacterial infections was quite similar to that of penicillin. Originally, streptomycin was injected every three to four hours. Experiments have shown that therapy is just as effective when the drug is administered infrequently as when it is given regularly every few hours. No data are available that would suggest any superiority or inferiority of intermittent therapy over treatment at regular intervals with paraminosalicylic acid, aureomycin, chloramphenicol, or terramycin.

It should be evident that these data presented by Marshall are concerned with general body infections, such as pneumonitis, and not with intraocular infections. The blood-aqueous barrier is less easily passed than the blood-lung barrier or other tissue barriers throughout the body except that of the blood and cerebrospinal fluid. Therefore, this difference must be kept in mind in ophthalmologic practice. It would appear that very large doses, perhaps intermittently administered, would allow peak levels of antibacterial action to be obtained in the blood stream, thus permitting a greater intraocular penetration. Leopold [18u] notes the poor effects of antibiotics in established intraocular infections and suggests a careful reconsideration of dosage schedules. He stressed the importance of obtaining high intraocular concentrations of the desired antibiotic. The favorable experience with subconjunctival injections of penicillin and of streptomycin, given once daily, in intraocular infections would be evidence in favor of the effectiveness of an intermittent therapy with these agents in intraocular infection.[3a]

Theodore [18e] and Mierecki [19] point out the possibility of contamination of ocular solutions and of ocular ointments. This danger must also be kept in mind in prescribing and directing the patient in the proper use of any antibiotic preparation.

CORTISONE AND CORTICOTROPIN (ACTH)

Corticotropin, Cortisone, and Other Steroid Hormones.—Within the past year more than 3,000 references have been published on the steroids and their activities.[32] A thorough analysis of many of these references can be found in Selye's "Annual Report on Stress." Selye's [32] concept of the diseases of adaptation suggest that the pathogenicity of many systemic and local irritants depends largely upon the function of the hypophyseal-adrenocortical system. This system may either enhance or inhibit the defense reaction of the body against stressor agents.

Schematically, Selye [33] represents the interrelation of the hypophysis, the adrenal cortex, and the peripheral target organs, as shown in Figure 1. The stressor agent, trauma or infection, acts directly upon the cells and produces damage. This, in turn, brings about a formal

32. Selye, H.: Annual Report on Stress, Montreal, Canada, Acta, Inc., Medical Publishers, 1951.

33. (*a*) Pentini, G.: The Eye and the General Adaptation Syndrome, Ann. ottal. e clin ocul. **77**:287, 1951. (*b*) Selye.[32]

defense by producing a stimulus which activates the anterior lobe of the pituitary to liberate corticotropin, and it may also cause the liberation of the somatotropic hormone (STH), the so-called growth hormone.

The nature of the stimulus which brings about activity of the anterior lobe of the pituitary that is, whether it is a humoral or a neural stimulant, is not yet known. In Figure 1 this is indicated merely by a dotted line with a question mark. Corticotropin, in turn, stimulates the adrenal cortex to produce predominantly glucocorticoid compounds, whose effect upon the response of the various target organs is generally inhibitory, that is, decrease in granuloma formation and in allergic responses and diminished resistance to infection. The glucocorticoids are highly potent in causing thymicolymphatic involution and in eliciting the characteristic changes in the blood cell count of the alarm reaction. Inflammatory granulomas are inhibited by the glucocorticoids. Conversely, the somatrotropic hormone produces a variety of defensive reactions in the target organ—that is, the building up of tissue, often stimulation of granulation-tissue formation and of allergic responses, and increased resistance to infection, primarily by

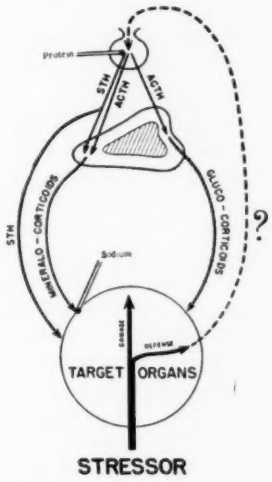

Fig. 1.—Schematic diagram illustrating the principal interrelations of the hypophysis, the adrenal cortex, and the peripheral target organs during the general adaptation syndrome. Reprinted, with permission, from Selye, H.: The Physiology and Pathology of Exposure Stress, Montreal, Acta endocrinologica, Inc., 1950.

stimulation of the connective tissue. Perhaps some of this action is mediated through the adrenal cortex, but the direct effect of the somatotropic hormone on connective tissue elements appears to be to sensitize these tissues to the actions of the mineralocorticoids. It is also likely that the somatotropic hormone brings about increased production of mineralocorticoids. Mineralocorticoids are the corticoids, such as desoxycorticosterone, which produce the experimental changes of so-called hypertensive and rheumatic diseases, notably atherosclerosis, hypertension, vascular disease, periarteritis nodosa (essential polyangiitis), and hyalonecrosis of arterioles, but does not produce any change in the thymicolymphatic tissues or the blood cell count. The somatotropic hormone itself cannot maintain the cortical cells in responsive conditions. Hence its corticotropic effect is dependent upon the simultaneous availability of corticotropin. It is evident, therefore, that the physiologic and pathologic effects of the response of the target organs to stress depends largely upon the balance between the mineralocorticoids and the somatotropic hormone, on the one hand, and corticotropin and glucocorticoids, on the other. High-protein diets increase the production of corticotropic hormones by the pituitary gland, as shown in the

diagram, whereas the action of the mineralocorticoids on the target organs is increased by the excess of sodium, which is also illustrated in Figure 1.

Selye [32] states that of the disturbances of the general adaptation syndrome which may cause disease, the most important is the absolute excess or deficiency in the amount of corticoids and of somatotropic hormone produced on stress—a disproportion in the relative secretion during stress of corticotropin and glucocorticoids, on the one hand, and of somatotropic hormone and mineralocorticoids, on the other. There is also the possibility that metabolic derangements may alter the response of the target organ to the hormones and that other organs which participate in this scheme, such as the nervous system, the liver, or the kidney, may also respond abnormally and become the responsible factor in the production of disease during adaptation to stress. There are several objections to this stress concept, most of which have been reasonably answered by Selye.[32]

Definition.—Corticoids have been defined by Selye [32] as the entire group of hormones which imitate the function of the adrenal cortex. Among these are the corticoids which have as their predominant activity the transformation of protein into carbohydrate and the deposition of the latter in the form of liver glycogen. These are called glucocorticoids. Other corticoids are relatively poor in this carbohydrate action but exert a powerful effect on water and electrolyte metabolism, and these Selye has designated as mineralocoricoids.

Liberation of Corticotropin.—The etiologic agents which are responsible for the liberation of corticotropin are trauma,[34] hemorrhage,[35] and temperature.[36] Auditory stimuli produce evidence of stress—the production of gastric ulcers, and various renal and cardiovascular lesions, as well as depletion of ascorbic acid in the adrenal glands of the rat. This phenomenon can be inhibited by demedullation of the adrenal by the use of adrenergic-blocking agents or the transplantation of pituitary tissue from its normal location into the anterior chamber of the eye. Increased oxygen pressure may also act as a stimulus to production of corticotropin.[37]

Drugs [38] may act as stimuli. Various adrenergic-blocking agents, such as dibenamine® (N-N-dibenzyl-B-chloroethyl amine), prove to be potent alarm stimuli, as judged by various indices of adrenocortical stimulation. Antibiotics, such as penicillin, streptomycin, and terramycin, can cause liberation of corticotropin, and perhaps this may contribute to their beneficial effects in the therapy of microbial diseases. Other agents which may produce liberation of corticotropin are the various fever-producing substances and salicylates.[39]

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39. Salicylates and Cortisone in Rheumatic Diseases, Lancet **1**:780, 1951.

Methods of Chemical Assay.—Many methods for the assay of these adrenocortical products have been suggested.[40a-c] A large portion of the urinary corticoids are present in a conjugated form, from which they can be liberated by enzymes, such as glucuronidase.[40a] One test employs phosphomolybdic acid, and it is stated that this test is suitable for the determination of lipid-soluble reducing corticoids in the plasma.[41] Another test employs blue tetrazolium BJ. (3,3′-dianisole *bis*-4-4′[3,5-diphenyl] tetrazolium chloride) for determination of corticoids having a primary α-keto side-chain.[42] Increasing attention has been paid recently to paper chromatography as a means of differentiating these adrenocortical products.[43] It is evident that for really accurate assessment several bioassay methods must be used, such as the adrenal-ascorbic-acid test in hypophysectomized rats, the changes in blood eosinophiles or lymphocytes, and the urinary excretion of 17-ketosteroids, uric acid, sodium, and potassium.[44]

Modes of Administration and Potential Dangers.—Corticotropin has its optimal effect when given more or less continuously, that is, every four to six hours intramuscularly day and night, but a definitely increased effectiveness has been demonstrated by intravenous drip techniques.[45] Intravenous administration of corticotropin, in addition to being cheaper, activates the adrenal gland in patients who are unresponsive to intramuscularly administered corticotropin and is capable of reactivating the adrenal cortex suppressed by cortisone therapy. Renold and co-workers [46] conclude that the clinical results obtained with intravenously administered corticotropin, 20 mg. daily, compare favorably with those obtained with doses of 5 or 10

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45. Gordon, E. S.; Kelsey, C., and Meyer, E. S.: Adrenal Stimulation by Intravenous ACTH, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 30. Kanee, A.: Corticotropin (ACTH) administered Intravenously, A. M. A. Arch. Dermat. & Syph. **65**:95, 1952. Jelliffe, A. M.; Steward, P. A., and Beaumont, G. E.: ACTH by Intravenous Infusion, Lancet **1**:1260, 1951. Mandel, W.; Singer, M. J.; Gudmundson, H. R.; Meister, L., and Modern, F. W. S.: Intravenous Use of ACTH, J. A. M. A. **146**:546, 1951.

46. Renold, A. E.; Forsham, P. H.; Maisterrena, J., and Thorn, G. W.: Intravenously Administered ACTH, New England J. Med. **244**:796, 1951.

times this amount given intramuscularly. An anaphylactic response to corticotropin administered intramuscularly may be the result of the adrenals failing to respond to stimulation, and it is suggested that one can avoid this reaction by changing from pork to beef corticotropin.[47]

The manifestations of overdosage with corticotropin and cortisone are similar to those reported last year—insomnia, euphoria, sudden fluctuations of mood, cerebral disturbance, psychotic personality, status-epilepticus changes, rounding of the face, acne, hypertrichosis, striae, "buffalo hump," rise in blood pressure, thrombotic complications, excessive water retention, hypopotassemia, decreased sugar tolerance, excessive catabolism, osteoporosis, and lowered resistance to infection. In renal disease, such as nephritis and nephrosclerosis, and in congestive heart disease, peptic ulcer, and hypertension these agents may be especially dangerous.[48]

As one becomes better informed on the fundamental mechanisms through which these hormones act, it becomes easier to administer them without serious side-effects. Thus, the manifestation of excessive sodium chloride and water retention can be counteracted by low-sodium intake. Results of hypopotassemia can be prevented by the administration of potassium.

Cortisone can be used locally in the form of drops or as an ointment in the eye; it may be given intramuscularly and may be taken by mouth. It is also possible, when tablets of cortisone are not available, to give injectable cortisone as a syrup by mouth.[49] Compound F (17-hydroxycorticosterone) may be given locally in the

47. Forsham, P. H.; Renold, A. E., and Frawley, T. F.: Nature of ACTH Resistance, Program of the Association for the Study of Internal Secretions, 33d Meeting, Atlantic City, N. J., 1951, p. 20. Rohm, E. N., Jr., and Hollander, J. L.: Allergy to ACTH in the Use of Beef ACTH, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 391.

48. (*a*) McLester, J. G.: Physiologic Effects, Contraindications, Dosage and Control of ACTH and Cortisone Therapy, J. M. A. Alabama **20**:319, 1951. (*b*) Proctor, E. L., and Rawson, E. J.: Adrenocortical Failure Following Treatment with Cortisone and ACTH, Am. J. Clin. Path. **21**:158, 1951. (*c*) Parmer, L. G.; Katonah, F., and Angrist, A. A.: Comparative Effects of ACTH, Cortisone, Corticosterone, Desoxycorticosterone, Pregnenolone, on Growth and Development of Infant Rats, Proc. Soc. Exper. Biol. & Med. **77**:215, 1951. (*d*) Frawley, T. F.: Recognition and Prevention of Complications of ACTH and Cortisone Therapy, A. M. A. Arch. Indust. Hyg. **3**:587, 1951. (*e*) Sulzberger, M.: Effects of ACTH and Cortisone on Certain Skin Diseases, J. Invest. Dermat. **6**:323, 1951. (*f*) Lourel, F. C.; Franklin, W.; Beale, H. D., and Scheller, I. W.: Occurrence of Convulsive Seizures During Treatment of Asthma with Cortisone Acetate, New England J. Med. **244**:49, 1951. (*g*) Dorfman, A.: Status Epilepticus Coincident with the Use of Pituitary Adrenocorticotropic Hormone, J. A. M. A. **146**:25, 1951. (*h*) Morrison, J. F.; Eimor, A. H.; Bazeley, P. L., and Thayer, J. H.: Antigenic Properties of Growth Hormone and ACTH, Nature, London, **169**:28, 1952. (*i*) Boland, E. W., and Headley, M. E.: Results of Long Continued Cortisone Administration in Rheumatoid Arthritis, California Med. **74**:416, 1951. (*j*) Engleman, E. P.; Kunkel, P.; Welsh, J. E., Jr., and Molyneaux, M. G.: Experiences with Cortisone Given Orally, ibid. Med. **75**:1, 1951. (*k*) Krupp, M. A.; Saier, M., and Keddie, F.: Experience with Cortisone and ACTH in Private Clinic, ibid. **75**:6, 1951. (*l*) Rowe, A., Jr.; Lamb, G. R.; Taylor, F. B., and Kinsel, L. W.: Experience with ACTH and Cortisone in Private Practice, ibid. **75**:11, 1951. (*m*) Cosgriff, S. W.: Thrombo-Embolic Complications Associated with ACTH and Cortisone Therapy, J. A. M. A. **147**:924, 1951.

49. Engelman, E. P.; Krupp, M. A., and Kunkel, P.: The Oral Use of Cortisone Suspension in Syrup, J. A. M. A. **145**:402, 1951. Boland, E. W., and Headley, N. E.: The Oral Use of Cortisone Acetate, ibid. **145**:8, 1951.

form of drops or as an ointment, or may be applied subconjunctivally.[50] It has been injected directly into joints.[51] It should be noted that newborn rats given large amounts of cortisone in the first week of life may exhibit a persistent stunting in growth, with failure to regain normal body weight three months after cessation of the injections. The younger the animal at the time of the first injection, the more marked is the disturbance in its growth.[48c] Congenital defects have been produced experimentally with cortisone.[52] Deaths have resulted from the use of cortisone and corticotropin in some infants.[53]

Differences in the action of corticotropin and that of cortisone are well known. There are the differences in the way the drugs can be given. Corticotropin can be given only systemically. Since it is a protein, it will be digested by the enzymes of the intestinal tract when given by mouth. Cortisone can be given orally, locally, or parenterally. The relation of the sweat-chloride concentration to the rate of sweating is decreased by desoxycorticosterone acetate and is not influenced, or is actually increased, by cortisone.[54] Corticotropin acts like desoxycorticosterone acetate. Compound F acts like cortisone.[55] Corticotropin produces a greater eosinopenic response than cortisone or Compound F. Corticotropin decreases blood cholesterol; cortisone and Compound F increase it. Corticotropin stimulates the secretion and the size of the adrenal cortex, whereas cortisone and Compound F inhibit the secretion and decrease the size of the adrenal cortex.

Special Preparations.—By special procedures it is possible to separate protein from ordinary corticotropin, particularly active fractions, which are 30 to 100 times as potent as the corticotropin standard. These products are less likely to elicit hypersensitivity reactions.[56] By absorption on colloidal neutralized gelatin[57] or

50. (*a*) Smith, R. W., Jr., and Steffensen, E. H.: ACTH and Cortisone in the Treatment of Arthritic Disease, New England J. Med. **245**:972, 1951. (*b*) McDonald, P. R.; Leopold, I. H.; Vogel, A., and Mulberger, R.: Evaluation of Compound F in Ocular Disease, Read at the Fourth Wills Hospital Clinical Conference, Philadelphia, March 22, 1952.

51. Hollander, J. L.; Brown, E. M.; Jessar, R. A., and Brown, C. Y.: Hydrocortisone and Cortisone Injected into Arthritic Joints, J. A. M. A. **147**:629, 1951.

52. Fraser, F. C.: Experimental Production of Congenital Anomalies, Canad. M. A. J. **64**:270, 1951. Experimental Production of Congenital Anomalies with Cortisone, editorial, J. A. M. A. **148**:206, 1952. Fraser, F. C., and Fainstat, T. D.: Production of Congenital Defects in the Offspring of Pregnant Mice Treated with Cortisone: Progress Report, Pediatrics **8**: 527, 1951.

53. Silverman, W. A.; Day, R. L., and Blodi, F. C.: Inhibition of Growth and Other Effects of ACTH in Premature Infants, Pediatrics **8**:177, 1951. Wilson, R., and Rowe, R.: Some Special Problems in the Use of ACTH and Cortisone Therapy in Children, J. Pediat. **40**:164, 1952.

54. Locke, W.; Talbot, N. B.; Jones, H. S., and Worcester, J.: Studies of the Combined Use of Measurements of Sweat Electrolyte Composition and Rate of Sweating as an Index of Adrenal Cortical Activity, J. Clin. Invest. **30**:325, 1951.

55. Conn, J. W.; Louis, L. H., and Fajans, S. S.: Probability That Compound F Is the Hormone Produced by the Normal Human Adrenal Cortex, Science **113**:713, 1951.

56. Forsham, P. H.; Renold, A. E., and Lesh, J. B.: Metabolic Effects of Small Molecular ACTH: A Preliminary Report, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 1, p. 7. Morrison and others.[48b]

57. Payne, R. W.; Rosenberg, I. N.; Raben, M. S.; Cleroux, A. P., and Astwood, E. B.: Effectiveness of Corticotropin Suspension, Program of the 43d Meeting of the American Society for Clinical Investigation, 1951, p. 44. Shulman, L. E.; Harvey, A. M. G.; Howard, J. A., and Schoenrich, E. H.: Clinical Studies with ACTH in Bronchial Asthma, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 401.

colloidal aluminum phosphate with polyvinyl-pyrrolidone,[58] it is possible to obtain long-acting corticotropin preparations, which obviate the necessity for multiple daily injections. Most of them, however, tend to produce local irritation at the site of injection. The purpose is to delay the absorption and to have the action of the hormone over a longer period.

Compound F.—Compound F was first described by Mason, Hoehn, and Kendall in 1938,[59] when they reported on the chemical structures of Compounds C, E, (cortisone), F, and G. Since that time approximately 28 steroids have been isolated from the adrenal cortex tissue. Only six of these have been shown to have important biological activity.[60] There is evidence that when the adrenal cortex is stimulated the predominant hormone liberated is Compound F.[61]

It has been suggested by Mason that Compound F is the principal corticoid with anti-inflammatory activity at tissue level.[62] Thorn and associates compared the eosinopenic activity of orally administered cortisone and Compound F, and found Compound F and its acetate more active than cortisone acetate. Compound F is definitely less active when administered orally than when administered intramuscularly.[63] Conn [64] found that free Compound F when given intramuscularly produced intense metabolic changes, whereas Compound F acetate had only mild effects, but free Compound F and Compound F acetate when given orally produced the same intense changes as those noted with free Compound F when given parenterally. The only apparent advantage of Compound F over cortisone for systemic therapy would be in acute cases in which a high level of circulating adrenal cortex hormone was required. Hollander's studies [51] suggest that Compound F is more effective than cortisone when injected locally into the joint in the therapy of rheumatoid arthritis. He suggests that the superior performance of Compound F is due to the fact that this substance is one-seventh as soluble as cortisone in plasma, thus

58. (*a*) Wolfson, W. Q.; Thompson, R. E.; Robinson, W. D.; Duff, I. F.; Cohn, C.; Lewis, L., and Hunt, H. D.: Development, Evaluation and Clinical Use of Long-Acting ACTH Preparations, in Mote, P. R.: Proceedings, Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 1. (*b*) Wolfson, W. Q.; Thompson, R. E.; Robinson, W. D.; Duff, I. F.; Cohn, C., and Lewis, L.: An Excellent Tolerated, Heat-Stable, Long-Acting ACTH Preparation Suitable for Prolonged and Ambulatory Treatment, Program of the 33d Meeting of the Association for the Study of Internal Secretions, Atlantic City, 1951, p. 80.

59. Mason, H. L.; Hoehn, W. N., and Kendall, E. C.: Chemical Studies of the Suprarenal Cortex, J. Biol. Chem. **124**:459, 1938.

60. Wolfson and others.[58b] Perera, G. A.; Ragan, C., and Werner, S. C.: Clinical and Metabolic Study of 17-Hydroxycorticosterone (Kendall Compound F): Comparison with Cortisone, Proc. Soc. Exper. Biol. & Med. **77**:326, 1951. Thorn, G. W.: Adrenals in Health and Disease, Tr. & Stud. Coll. Physicians, Philadelphia **19**:95, 1952.

61. Mason, H. L.: Isolation of Adrenal Cortical Hormones from Urine, J. Biol. Chem. **182**:131, 1950.

62. Mason, H. L.; Nelson, D. H.; Reich, H., and Samuels, L. D.: Isolation of Steroid Hormone from the Adrenal Vein Blood of Dogs, Science **111**:578, 1950. Boland, E. W., and Headley, M. E.: Compound F Used Orally in Patients with Rheumatoid Arthritis. J. A. M. A. **148**:981, 1952. Jacobsen, R. P., and Pincus, G.: The Chemistry of Adrenal Steroids, Am. J. Med. **10**:531, 1951. Perera, G. A.; Ragan, C., and Werner, S. C.: Clinical and Metabolic Study of 17-Hydroxycorticosterone (Kendall's Compound F): Comparison with Cortisone, Proc. Soc. Exper. Biol. & Med. **77**:326, 1951.

63. Thorn, G. W.; Renold, A. P.; Wilson, D. L.; Frawley, F. F.; Jenkins, D.; Garcia-Reyes, J., and Forsham, P. H.: Clinical Studies on the Activity of Orally Administered Cortisone, New England J. Med. **245**:549, 1951.

64. Conn and others.[55] Conn, J. W.; Louis, L. H.; Fajans, S. S.; Johnson, B. J.; Barott, G. W.; Hogg, L. W.; Blood, J. P., and Weiss, M.: Metabolic Effects in Man of Orally and Parenterally Administered Compound F and Compound F Acetate, Proc. Centr. Soc. Clin. Res. **24**:23, 1951.

establishing a reservoir of the Compound F which might remain in the joint space and give alleviation of symptoms over a longer period. Hollander and others,[51] Smith and Steffensen,[50a] and McDonald, Leopold, and others [50b] have shown that Compound F is as effective as cortisone in ocular inflammations. McDonald and associates [50b] demonstrated certain cases in which Compound F was superior to locally instilled cortisone in some ocular disorders, particularly vernal conjunctivitis. Experimental studies revealed no significant difference between the two compounds. The last-mentioned authors used Compound F suspended in 1: 10,000 benzalkonium chloride, 1 part of Compound F to 4 parts of benzalkonium chloride solution, for drop instillation and injected 1.25 to 2.5 mg. subconjunctivally.

Influence of Steroids on Capillary Permeability, Inflammation, and Spreading Factors.—Evidence has continued to pile up showing that the somatotropic hormone stimulates the rate of formation of granulation tissue, as does thyroxin, and that corticotropin and cortisone inhibit this granulation-tissue formation.[65] There is further evidence that corticotropin decreases capillary permeability which has been

65. (*a*) Shechmeister, I. L., and Pond, P. P.: Response of Mice to Inoculation with Certain Avirulent Bacteria After Exposure to Sublethal Total Body X-Ray, Federation Proc. **10**:418, 1951. (*b*) Rebuck, J. W.; Smith, R. W., Jr., and Margulis, R. P.: ACTH and Leukocytic Performance in Windows in Man, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 1, p. 460. (*c*) Opsahl, J. C.; Long, C. N. H., and Fry, E. G.: Chorionic Gonadotropin, ACTH and Adrenal Hyaluronidase Relationship, Yale J. Biol. & Med. **23**:399, 1951. (*d*) Menkin, V.: Effect of Commercial Cortisone Acetate Suspension on Capillary Permeability, Am. J. Physiol. **164**:294, 1951. (*e*) Martin, S. P.; Bennett, I. L., and Chaudhuri, S.: The Effect of a Series of Bacteria and Their Products on the Human Leukocyte, Program of the 43d Meeting of the American Society Clinical Investigation, 1951, p. 38. (*f*) Anderson, G. E.; Wiesel, L. L.; Hillman, R. W., and Stump, W. N.: Sulfhydryl Inhibition as a Mechanism in the Effects of ACTH and Cortisone, Proc. Soc. Exper. Biol. & Med. **76**:825, 1951. (*g*) Smith, D. T., and Reinmuth, O. M.: Effect of ACTH on Pneumonia Induced with Tuberculin in Lungs of Sensitized Rabbits, Federation Proc. **10**:4, 1951. (*h*) Garmuth, F. G., Jr.; Nedcel, G. A.; Ottinger, B., and Oyama, J.: Anatomic and Histologic Changes in Rabbits with Experimental Hypersensitivity Treated with Compound E and ACTH, Proc. Soc. Exper. Biol. & Med. **76**:177, 1951. (*i*) O'Neill, G. Q.; Ford, R. T.; Dughi, D. N., and Faddis, E.: A Critique of Laboratory Methods for the Evaluation of Agents for Use in Collagen Diseases, Federation Proc. **10**:328, 1951. (*j*) Sutliff, W. D., and Norman, S. L.: Adrenocorticotropic Hormone in Cutaneous and Systemic North American Blastomycosis, in Mote, J. R.: Proceedings Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 391. (*k*) Ungar, G., and Damgaard, E.: Studies on Fibrinolysin-Antifibrinolysis System in Serum: Action of Anterior Pituitary, Adrenal Cortex and Spleen, J. Exper. Med. **93**:89, 1951. (*l*) Ungar, G.; Damgaard, E., and Weinstein, H. P.: Anaphylactic Arthritis in Guinea Pigs and Its Hormonal Control, Federation Proc. **10**:422, 1951. (*m*) Selye, H.: Role of Somatotropic Hormone in the Production of Malignant Nephrosclerosis, Periarteritis Nodosa, and Hypertensive Disease, Brit. M. J. **1**:263, 1951; (*n*) The Effects of the Local Injection of Electrophoretically Pure Somatotropic Hormone, Rev. canad. biol. **9**:476, 1951; (*o*) The Physiology and Pharmacology of the 11-Desoxysteroids, Program of the Steroid Hormone Conference, México, D. F., Philadelphia, The Blakiston Company, 1951. (*p*) Reid, E.: Assay of Diabetogenic Pituitary Preparations, J. Endocrinol. **7**:120, 1951. (*q*) Selye, H.: Influence of STH, ACTH and Cortisone upon Resistance to Infection, Canad. M. A. J. **64**:49, 1951. (*r*) Adams, F. H.; Berglund, E.; Balkan, S. G., and Chisholm, P.: Pituitary Adrenocorticotropic Hormone in Severely Burned Children, J. A. M. A. **146**:31, 1951. (*s*) Adams, F. H.; Berglund, E., and Tamerin, J. A.: ACTH in Burns, ibid. **145**:925, 1951. (*t*) Whitelaw, M. J.: Physiological Reaction to Pituitary Adrenocorticotropic Hormone (ACTH) in Severe Burns, ibid. **145**:85, 1951. (*u*) Frawley, T. F.; Roche, N.; Jenkins, D., and Thorn, G. W.: The Role of the Pituitary Adrenocortical System in the Response to Anoxia, Program of the 43d Meeting of the American Society for Clinical Investigation, 1951, p. 17.

brought on by hyaluronidase; likewise, the migration of leucocytes, normally stimulated by a variety of bacterial products, can be inhibited by pretreatment with corticotropin. There is evidence of clear-cut antagonism between the somatotropic hormone, which increases the inflammatory potential of connective tissue, and somatotropic hormone or cortisone, which decreases it.[65a] Somatotropic hormone administered in the form of an electrophoretically pure preparation caused pronounced connective-tissue proliferation at the site of injection, showing numerous immature fibroblasts, with rather basophilic cytoplasm, and increased collagen-fiber formation. In the capillaries and small arterioles at the site of injection there was marked hyperplasia of large endothelial cells. Curiously, all these manifestations were more pronounced if the somatotropic hormone was injected into the joint region than when it was introduced elsewhere into the connective tissue.[65l-n] Somatotropic hormone possesses a number of desirable pharmacologic effects, quite apart from its action upon somatic growth. It stimulates encapsulation of bacterial foci by granulomatous tissue and greatly increases resistance to certain infections.[65o] However, somatropic-hormone preparations are not yet commercially available and possess unpleasant side-effects, such as diabetogenic potency and a tendency to produce hypersensitivity reactions. Most of the somatotropic hormone which has been tested to date has been impure.[65p]

The mechanism through which corticotropin and cortisone diminish resistance to infection is not yet clearly understood, but theoretical considerations led Selye to suspect that the inhibitory effect of these hormones on granuloma formation and the consequent encapsulation of infectious foci, their destructive effect on lymphatic tissue, and their general catabolic effect might be involved. Since in all these respects the somatotropic hormone acts as an antagonist to corticotropin, he felt that it would be of interest to establish by animal experiments whether this hormone could raise resistance to infection. Experiments performed on rats revealed that both cortisone and corticotropin when given in toxic doses can result in fatal systemic infections, which are presumably due to otherwise nonpathogenic microorganisms normally present in the body. This effect of cortisone and corticotropin can be completely prevented by suitable doses of purified somatotropic hormone.[65q]

Influence of Hormones on Body Resistance.—It is suggested by Selye[65a'] that somatotropic hormone and the mineralocorticoids may raise resistance wherever increased fibroplasia and encapsulation are advantageous, as in pulmonary tuberculosis and other rapidly spreading infections, in wound healing, and in the atrophy of connective tissue due to age. Spectacular results following the use of corticotropin in the treatment of burns in man have been reported.[65r,s] The tolerance to anoxemia has been increased by pretreatment with corticotropin.[65u] This observation would appear to be of more than passing interest because of the recent suggestion of the role of anoxia in the production of retrolental fibroplasia. A reevaluation of corticotropin therapy in retrolental fibroplasia with anoxia in mind might be of value.[65b']

Influence of Corticotropin on Infectious Diseases.—In mice and rats infected with Pneumococcus, the influenza virus, rickettsiae or Salmonella typhosa, corticotropin therapy caused no significant change in resistance, as judged by survival.[66] Animal experimentation by Woods and

65a'. Selye, footnotes 65 m, n, o, q.

65b'. Lanman, J. T.; Guy, L. P., and Dancis, L.: Adrenocorticotropic Hormone in the Therapy of Retrolental Fibroplasia, Pediatrics **9**:27, 1952.

66. Finland, M.; Kass, E. H., and Ingber, S. H.: Further Observations on the Effects of ACTH, in Mote, J. R.: Proceedings of Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 1, p. 478. Kass, E. H., and Finland, M.: Role of Adrenal Steroids in Infection and Immunity, New England J. Med. **244**:464, 1951.

Wood[67] indicates that corticotropin, cortisone, and Compound F are contraindicated in ocular tuberculosis. Mice infected with tuberculosis showed a shorter mean survival time than did untreated controls, but if these animals were given streptomycin, additional treatment with corticotropin did not alter the course of the tuberculosis.[68] Adrenalectomy decreases resistance to various experimental infections, and corticoid therapy compensates for this defect. It has also been shown that this action may be correlated in part with the effect of bacteria upon the hyaluronidase system.[69] Adrenalectomy shortens the survival time following x-irradiation, and this survival time can be increased by the use of adrenal cortex extracts.[70] In mice, guinea pigs, and rabbits infected with various types of Brucella, the death rate was increased and the lesions were much more widely distributed after the use of cortisone.[71] Smith and Opsahl's experiments[69] have shown that when mice were infected with a hyaluronidase-containing bacterium, such as Micrococcus pyogenes var. aureus, and a hyaluronidase-free bacterium, such as a derivative of Salmonella, the corticotropin extract strikingly inhibited the course of the infection by the bacterium containing hyaluronidase, both in normal and in adrenalectomized animals. When the extract was mixed with the bacterial suspension prior to intradermal injection, the course of the infection was even more effectively inhibited. In the case of the hyaluronidase-free bacteria, the protective effect of the adrenal cortex extracts could be demonstrated only in adrenalectomized animals, whose otherwise subnormal resistance was raised toward normal.

Mogabgab and Lewis[72] have demonstrated that cortisone definitely reduces the ability of animals to withstand staphylococcic infection. They suggest that this loss of resistance results from the reduction of local inflammatory reaction, perhaps through depletion of lymphoid cells in the blood stream and in the tissues. Any reduction of permeability would make it more difficult for defense mechanisms to get to the site of infection. These authors were unable to demonstrate any impairment of phagocytosis, interference with antibody formation, or reduction in penicillin effect by virtue of the administration of cortisone. Desoxycorticosterone acetate did not block increase in severity of the streptococcic disease by cortisone.

Considerable evidence has been presented warning of the dangers of use of cortisone and corticotropin in tuberculosis.[73]

Cortisone facilitates the development of experimental poliomyelitis infection in hamsters. Corticotropin, desoxycorticosterone acetate, progesterone, and diethylstilbesterol failed to modify such poliomyelitis infections.[74]

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67. Woods, A. C., and Wood, R. M.: Studies in Experimental Ocular Tuberculosis, A. M. A. Arch. Ophth. **47**:477, 1952.

68. Svedberg, B.; Dahlstrom, B., and Luft, R.: Effect of Adrenocorticotropic Hormone (ACTH) on Experimental Tuberculosis in Mice: Preliminary Report, Acta endocrinol. **60**:50, 1951.

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70. (*a*) Edelmann, A., and Katsh, S.: Survival of Rats Adrenalectomized After X-Ray Irradiation, Federation Proc. **10**:38, 1951. (*b*) Katsh, S., and Edelmann, A.: Adrenal Cortical Requirements of Adrenalectomized X-Ray Irradiated Rats, ibid. **10**:73, 1951.

71. Abernathy, R.: Effect of Cortisone on Experimental Brucellosis, Program of the 43d Meeting of the American Society Clinical Investigation, 1951, p. 5.

72. Mogabgab, W. J., and Lewis, T.: Effects of Cortisone on Bacterial Infection, J. Lab. & Clin. Med. **39**:271, 1952.

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74. Swartzman, G., and Fisher, A.: Alteration of Experimental Poliomyelitis Infection in the Syrian Hamster with the Aid of Cortisone, J. Exper. Med. **95**:347, 1952.

Cortisone will protect mice against infection with Salmonellla typhimurium, but it is not as effective as chloramphenicol.[75]

Role of Corticotropin in the Aging Process.—There is no doubt that connective tissue plays an important part in those processes which are generally regarded as characteristic of aging. The diminished elasticity of the skin, the decreased inflammatory potential of connective tissue, slow healing of wounds, and the degradation of bone are characteristic of senility.[32] Furthermore, in the aged, protein catabolism tends to predominate over protein anabolic processes. The reverse of all this is typical of the growing child. Hence, it is interesting to note that animals treated with large doses of somatotropic hormone respond with tissue changes which are, generally speaking, the reverse of those characteristic of senility.[65o] It remains to be seen whether somatotropic-hormone deficiency plays any role in physiologic senility, and whether exogenous administration of this hormone could counteract some of the characteristic deficiencies of advanced age.[76]

Influence of Corticotropin and Cortisone on Body Temperature.—It has been well known for the past few years, and reaffirmed in the literature of the past year, that corticotropin and cortisone tend to combat the fever incident to a variety of diseases and to the injection of bacterial pyrogens and to dinitrophenol.[77] However, it has been demonstrated that cortisone actually prolonged fever in some cases of streptococcic infections.[78]

Effect on Blood Sugar.—Desoxycorticosterone depresses the fasting blood sugar in man.[79] Desoxycorticosterone increases the glucose in the aqueous humor and decreases that in the lens.[80] Evidence continues to accumulate demonstrating that corticotropin, cortisone, and Compound F tend to increase the blood sugar and to cause glycogen deposition in the liver. The diabetogenic effect is usually mild in normal man, but in persons with latent manifestations of diabetes these hormones tend to increase the hyperglycemia and the glycosuria and may induce some degree of insulin resistance.[81]

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80. Pentini, G., and Formaro, L.: The Eye in the General Adaptation Syndrome, Folia endocrinol. **3**:893, 1951.

81. (*a*) Rich, A. R.; Bennett, I. L.; Cochran, T. H.; Griffith, P. C., and McGoon, D. C.: Effect of ACTH and Cortisone upon Experimental Anaphylactic Glomerulonephritis, Bull. Johns Hopkins Hosp. **88**:189, 1951. (*b*) Sheltar, M. R.; Schmidt, H. L.; Lincoln, R. B.; DeVore, J. K.; Bullock, J. A., and Hellbaum, A. A.: Response of Serum Polysaccharide Fractions and Protein Fractions Following Cortisone Treatment, J. Lab. & Clin. Med. **39**:372, 1952. (*c*) Balmain, J. H.; Folley, S. J., and Glascock, R. F.: Inhibition of Fatty Acid Synthesis in Rat Mammary Gland Slices by Cortisone in Vitro and Its Antagonism by Insulin, Nature, London, **169**:447, 1952. (*d*) Layton, L. L.: Effects of Cortisone upon Chondroitin Sulphate Synthesis by Animal Tissues, Proc. Soc. Exper. Biol. & Med. **76**:596, 1951. (*e*) Adams, F. H.; Kelley, B. G.; Dwan, P. F., and Glick, D.: Response to Serum Hyaluronidase Inhibitor and Mucoproteins to Adrenocorticotropic Hormone in Rheumatic States, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 572; (*f*) Response of the Serum Hyaluronidase Inhibitor and Mucoproteins to Adrenocorticotropic Hormone in Rheumatic States: Mucolytic Enzyme Systems, 15, Pediatrics **7**:472, 1951.

The somatotropic hormone tends to produce hypoglycemia in acute experiments, presumably because it causes glycogen storage and increases the utilization of carbohydrates for growth. The effect cannot be due exclusively to increased insulin production, since it is manifest even in alloxanized and pancreatectomized animals. According to Meyer and Rappaport,[82] the serum polysaccharides tend to rise during stress and in the collagen diseases, while corticotropin and cortisone tend to restore their blood levels to normal. It has been shown that the serum nonglucosamine polysaccharides, glucosamine polysaccharides, albumin polysaccharides, α-globulin polysaccharides, and serum heat-coagulation values were decreased and that the albumin and the albumin-globulin ratio increased after cortisone treatment in the rheumatic patient.[81b] This action is further evidence that these agents may play a role in the pathogenesis and therapy of connective tissue diseases. It has been suggested by Layton [81d] that the palliative action of cortisone in connective tissue diseases may be due to its inhibitory effect upon the synthesis of the chondroitin sulfate structure of the connective-tissue ground substance.

Wound Healing.—It was found that cortisone had no inhibitory effect upon tissue culture in concentrations comparable to, and even 25 times as great as, the usual therapeutic levels. However, by exceeding these levels, one could inhibit growth.[83] Maumenee,[84] by virtue of his experimental studies, suggests that the use of cortisone prophylactically, or of corticotropin, will reduce the opacification of corneal grafts which appear to result from a sensitization to donor material. If the corneal tissue could be protected for approximately six weeks, the graft will assume the individuality of the recipient. Thus, the opacification of grafts which will result from this type of allergic reaction might be averted, even though the effect of cortisone lasts only while the drug is being administered. Newell and Dixon [85] found that subconjunctival injection of cortisone in rabbits receiving homologous corneal transplantation was associated with a delay in wound healing, with failure of keratoblastic proliferation. No inhibition of epithelial proliferation was observed in this study. Baxter and co-workers [86] describe a failure of homografts to survive even with corticotropin or cortisone therapy.

Although experimental evidence still indicates a retardation of wound healing by corticotropin and cortisone,[87] it is important to realize that with the usual dosage schedules ocular wounds heal satisfactorily. The patient's serum proteins are important in this regard.[88] Cortisone affects wound healing and mitosis essentially in the same manner as does corticotropin.[87a] Fornaro [89] studied the action of desoxycorticosterone acetate and corticotropin in the process of repair of experimental aspetic corneal wounds in the rabbit eye. Desoxycorticosterone acetate accelerated the process of cicatrization and of repair by conjunctival tissue, while corticotropin had an inhibitory effect. Both hormones were ineffective when the corneal wounds were superficial. Fornaro [90] has shown also that desoxycorticosterone acetate will produce

82. Meyer, K., and Rappaport, T. M.: The Mucopolysaccharides of the Brown Substance of Connective Tissue, Science **113**:596, 1951.

83. Steen, A. S.: Effect of Cortisone on Tissue Cultures, Brit. J. Ophth. **35**:741, 1951.

84. Maumenee, E.: Influence of Donor Recipient Sensitization of Corneal Grafts, Am. J. Ophth. **34**:142, 1951.

85. Newell, F. W., and Dixon, J. M.: Effect of Subconjunctival Cortisone upon the Immediate Union of Experimental Corneal Grafts, Am. J. Ophth. **34**:977, 1951.

86. Baxter, H.; Schiller, C.; Whiteside, J. H., and Straith, R. E.: Effect of ACTH on Survival of Homografts in Man, Plastic & Reconstruct. Surg. **7**:492, 1951.

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88. Findlay, C. W., Jr., and Howes, E. L.: Combined Effect of Cortisone and Partial Protein Depletion on Wound Healing, New England J. Med. **246**:597, 1952.

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90. Fornaro, L.: The Eye in the General Adaptation Syndrome, Rass. ital. ottal. **21**:28, 1951.

the development of connective-tissue sclerosis of the ciliary processes and that this can be inhibited in part by the simultaneous administration of corticotropin in the rat eye. Conway and Stark [91] reveal that corticotropin reduced keloid formation in keloid-prone persons, and even softened keloids when injections of cortisone and hyaluronidase were made into the base of existing keloids. The effect was not very great, however.[92]

The principal action of cortisone on homografts is to retard the development of immunity toward them. Cortisone also has a slight effect in preventing the local expression of the immune state. Thus, the life of homografts in rabbits can be prolonged by the local application of cortisone acetate. Recent clinical trials, however, discourage the use of corticotropin and cortisone in skin grafts.[93]

Neoplasms.—Lymphoid and connective-tissue tumors appear to be most sensitive to inhibition by corticotropin or cortisone.[94] There is evidence that patients with neoplasm may show abnormal types of steroids in the urine, but the urinary excretion of cortisone and Compound F is found to be the same in patients with various malignant tumors as in normal persons.[94e] Observations [94j] indicate that hormones (corticotropin and cortisone) or folic-acid antagonists are effective in producing further remission in approximately 50% of patients with leukemia showing resistance to one type of therapy. This suggests that corticotropin and cortisone have a different primary mode of action on leukemic processes from that of folic-acid antagonists.

Relation of Lipoproteins to Corticotropin or to Corticotropin and Cortisone.—Because some investigators have noticed a rise in serum cholesterol after administration of cortisone, a possible relation of cortisone and corticotropin to atherosclerosis has been suggested. It has been shown by Gofman and his co-workers that atherosclerosis could be correlated with the giant cholesterol-containing lipoproteins, Class SF10-20. Experimenters have been able to

91. Conway, H., and Stark, R. B.: ACTH in Plastic Surgery, Plast. & Reconstruct. Surg. **8**:354, 1951.

91a. Spain, D. M.; Molomut, N., and Haber, A.: Studies of the Cortisone Effects on the Inflammatory Response, J. Lab. & Clin. Med. **39**:383, 1952.

92. Conway, H., and Stark, R. B.: Corticotropin (ACTH) in Treatment of Keloids, A. M. A. Arch. Surg. **64**:47, 1952.

93. Billingham, R. E.; Krohn, P. L., and Medawar, P. M.: Effect of Locally Applied Cortisone Acetate on Survival of Skin Homografts in Rabbit, Brit. M. J. **2**:1049, 1951. Skin Homografts in Clinical Practise, editorial ibid. **2**:1073, 1951.

94. (*a*) Tompkins, E. H.: The Response of Monocytes to Adrenal Cortical Extract, J. Lab. & Clin. Med. **39**:365, 1952. (*b*) Schulman, I.; Lanman, J. T.; Laxdal, O. E., and Holt, L. E., Jr.: Effects of ACTH and Cortisone on Leukemia in Childhood, Pediatrics **8**:34, 1951. (*c*) Dobriner, K.: Adrenal Function in Steroid Excretion in Disease, in Symposium on Steroids in Experimental and Clinical Practice, Philadelphia, The Blakiston Company, 1951, p. 130. (*d*) Burton, R. B.; Zaffaroni, A.; Izzo, A. J., and Kutmann, E. H.: Studies on the Nature of the Adrenal Cortical Excretion in Patients with Malignancy, Program of the 43d Meeting American Society Clinical Investigation, 1951, p. 11. (*e*) Funk, C.; Tomashefsky, P.; Soukup, R., and Ehrlich, A.: Effect of the Hormonal Factors on Growth of a Transplanted Rat Tumor, Federation Proceedings **10**:185, 1951. (*f*) Alpert, L. K.; Zimmerman, J., and Cherr, E. H.: Effects of ACTH, Cortisone and Nitrogen Mustard on Malignant Diseases, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 235. (*g*) Farber, S.; Downing, V.; Schwachman, H.; Toch, R.; Appleton, R.; Held, F.; King, J. P., and Feriozi, D.: Action of ACTH and Cortisone on Children with Disseminate Cancer, in Mote, J. R.: Proceedings Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 226; (*h*) The Action of ACTH and Cortisone in Acute Leukemia, in Mote, J. R.: Proceedings Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 251. (*i*) Cummings, M. M.; Drummond, M. C.; Michael, M., Jr., and Bloom, W. L.: Influence of Cortisone on Artificially Induced Peritoneal Exudates, Bull. Johns Hopkins Hosp. **90**:185, 1952. (*j*) Pillers, E. N. K.; Burchenal, J. H.; Eliel, L. P., and Pearson, O. H.: Resistance to Corticotropin Cortisone, and Folic Acid Antagonists in Leukemia, J. A. M. A. **148**:907, 1952.

produce changes in the serum lipoproteins in the human subject and in the rabbit with corticotropin and cortisone, but no change could be demonstrated in lipoproteins SF10-20.[95]

Relation of Hormones to Antibody Formation.—Investigators for years have been interested in the relation of the adrenal gland to antibody formation. Observations on animals have frequently led to conflicting results. Reports have variously stated that corticotropin or cortisone has resulted in elevation, in no change, or in depression[96] of antibody levels in acute experiments.

Suppressive Effect of Hormones.—An imposing body of evidence shows that cortisone and corticotropin can suppress inflammatory reactions to a wide variety of stimuli,[97] including acute

95. (*a*) Adlersberg, D.; Schaefer, E., and Drachman, S. R.: Development of Hypercholesteremia During Cortisone and ACTH Therapy, J. A. M. A. **144**:969, 1950; (*b*) Studies on Hormonal Control of Serum Lipid Partition in Man, J. Clin. Endocrinol. **11**:67, 1951. (*c*) Bloom, B., and Pierce, F. T., Jr.: Relationship of ACTH and Cortisone to Serum Lipoproteins in Atherosclerosis in Humans, Metabolism **1**:155, 1952. (*d*) Pierce, F. T., Jr., and Bloom, B.: Relationship of ACTH and Cortisone to Serum Lipoproteins of the Rabbit, ibid. **1**:163, 1952. (*e*) Stanier, J.; Pick, R., and Katz, L. N.: Effects of Desoxycorticosterone Acetate on Cholesterolemia, Blood Pressure and Atherogenesis in Chicks, Circulation **4**:262, 1951.

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97. (*a*) Kass, R. H., and Finland, N.: Role of Adrenal Steroids in Infection and Immunity, New England J. Med. **244**:464, 1951. (*b*) Sprague, R. G.: Cortisone and ACTH: A Review of Certain Physiologic Effects and Their Clinical Implications, Am. J. M. Sc. **10**:567, 1951. (*c*) Witlow, N. J.: Treatment of Severe Burns with ACTH, in Mote, J. R.: Proceedings of Second Clincial ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 322. (*d*) Ebert, R. H., and Wissler, R. W.: In Vivo Observations of the Effects of Cortisone on the Vascular Reaction to Large Doses of Horse Serum, Using the Rabbit Ear Chamber Technique, J. Lab. & Clin. Med. **38**:499, 1951. (*e*) Elliott, K. A. C., and Yrarrazaval, S.: An Effect of Adrenalectomy and Cortisone on Tissue Permeability in Vitro, Nature, London **169**: 460, 1952. (*f*) Spain, Molomut, and Haber.[91a] (*g*) States, editorial, ACTH, Cortisone and Hypersensitive Disease Ann. Int. Med. **36**:911, 1952. (*h*) Wedgewood, R. J.; Ajwn, C. B. Z., and Janeway, C. A.: The Mechanism of Action of ACTH in Experimental Nephritis Due to a Foreign Protein, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 1, p. 108. (*i*) Grob, D.; Schoenrich, E. H.; Winkenwerder, W. C., and Harvey, A. M.: Influence of ACTH on the Reactivity of the Bronchial Tree, Skin and Secretory Glands to Specific Antigens, Histamine and Mecholyl in Bronchial Asthma, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 1, p. 499. (*j*) Grace, H. W.; Frank, L., and Wyse, R. J.: Effect of Cortisone upon Hypersensitivity Due to Lymphogranuloma Venereum, A. M. A. Arch. Dermat. & Syph. **65**:348, 1952. (*k*) Ehrich, W. E.: The Nature of Collagen Diseases, Am. Heart J. **43**:121, 1952. (*l*) Rantz, L. A.; Creger, W. C., and Choy, S. H.: Immunological Hyperreactivity in the Pathogens of Rheumatic Fever and Other Diseases, Am. J. Med. **12**:115, 1952. (*m*) Holman, J., and Goth, A.: Histamine Release in the Human Skin and the Effect of Cortisone, Federation Proc. **11**:358, 1952. (*n*) Winter, C. A., and Flataker, L.: Cortisone and Related Hormones: Effect on Response to Analgesic Drugs, J. Pharmacol. & Exper. Therap. **103**:93, 1951. (*o*) Goth, A.; Holman, J., and Copenhaver, J. H.: Mechanism of Action of Cortisone in Experimental Hypersensitivity, Federation Proc. **11**:349, 1952. (*p*) Thomas, L., and Good, R. A.: The Effect of Cortisone on the Schwartzman Reaction, J. Exper. Med. **95**:409, 1952. (*q*) Goldman, L.; Preston, R., and Rockwell, E.: The Local Effect of 17-Hydroxycorticosterone 21-Acete in the Diagnostic Patch Test Reaction, J. Invest. Dermat. **18**:89, 1952. (*r*) Ebert, R. H., and Wissler, R. W.: The in Vivo Observations of Vascular Reactions to Large Doses of Horse Serum Using Rabbit Ear Chamber Technique, J. Lab. & Clin. Med. **38**:511, 1951.

infant infections, wound healing, the Shwartzman phenomenon, chemical irritation, and thermal burns. All this evidence continues to demonstrate the nonspecificity of the suppressive effects of cortisone and corticotropin.[97] As mentioned above, there is at present no general agreement on the role of corticotropin and cortisone in the alteration of antibody formation and no positive evidence that antibody formation is suppressed in tuberculous infection. Similarly, cortisone does not appear to inhibit antigen-antibody union, at least in vitro.

Since cortisone tends to reduce the reactivity of the small blood vessels, as shown by Ebert and Wissler and others,[97d] it is apparent that disease states will be favorably or unfavorably affected according to the usefulness of the inflammatory response to the host. In wound healing and in acute infections the inflammatory reaction is useful to the host and, as might be expected, the effects of cortisone are unfavorable. In rheumatic fever, rheumatoid arthritis, and certain allergic states the inflammatory reaction appears to have no value to the host, and the effect of cortisone or corticotropin is beneficial. Tuberculosis poses a complex problem, as I have briefly discussed above. On theoretical grounds, one might expect a reduction of tissue destruction, together with poorer localization of tubercle bacilli. It is obvious from the experiments of Ebert and Wissler,[97d] however, that caseation is not suppressed. It is possible that the reduction in exudate results in greater multiplication of infecting organisms; so even though the ability of the tissue to react is quantitatively reduced, the stimulus to reaction is greater. This reaction would also explain the apparent flare-up of infection after therapy is stopped.

Probably no absolute answer on the harmfulness or usefulness of cortisone in tuberculous is possible at the present time. Results seem to vary according to the number and virulence of infecting organisms, the degree of hypersensitivity and immunity, the dose of cortisone, and the organ involved. In general, however, a drug which can profoundly reduce inflammation is a potential danger in any infection, particularly since the harmful effects may not be apparent until after cortisone treatment has been stopped.

Cortisone, Compound F, and Corticotropin in Ocular Disease.—Cortisone or corticotropin administered parenterally, or topical administration of cortisone or "hydrocortisone," is of dramatic benefit in the inflammatory and exudative phases of several inflammatory conditions, notably those affecting the cornea, uveal tract, and external portion of the eye.[98-102] As pointed out clearly by Woods,[98a] this

98. (*a*) Woods, A. C.: The Present Status of ACTH and Cortisone in Clinical Ophthalmology, Am. J. Ophth. **34**:945, 1951. (*b*) Dickey, R. L.: Cortisone and ACTH in the Treatment of Diseases of the Eye, Delaware M. J. **23**:11, 1951. (*c*) Henderson, J. W., and Hollenhorst, R. W.: Clinical Observations on the Use of Cortisone in Ophthalmic Diseases, Tr. Am. Acad. Ophth. **55**:543, 1951. (*d*) Moutinho, H., and Vasto, O. P.: Ocular Therapy with Local Applications of Cortisone, A. M. A. Arch. Ophth. **11**:241, 1951. (*e*) Berens, C., and Girard, L. J.: ACTH and Cortisone, J. Florida M. A. **37**:695, 1951. (*f*) McLean, J. M.: Present Status of ACTH and Cortisone in Treatment of Eye Diseases, Sight-Saving Rev. **21**:67, 1951. (*g*) Hill, H. F.; Dennis, R. H., and Shannon, E. G.: ACTH and Cortisone in Ophthalmology, J. Maine M. A. **42**:47, 1951. (*h*) Krupp, M. A.; Saier, M.; Keddie, F.; Tanner, R., and Snell, A. M.: Experience with Cortisone and ACTH in a Private Clinic, California Med. **75**:6, 1951. (*i*) Rowe, A., Jr.; Lamb, G. R.; Taylor, F. B., and Kinsell, L. W.: Experience with ACTH and Cortisone in Private Practice, ibid. **75**:11, 1951. (*j*) Paich-Szanto, O.: The Intermittent Form of Sympathetic Ophthalmitis and Its Therapy, Klin. Monatsbl. Augenh. **118**:499, 1951. (*k*) Laws, H. W., and Howard, R. P.: Sympathetic Ophthalmia Treated Successfully with ACTH, Canad. M. A. J. **64**:530, 1951. (*l*) Vesterdal, E.: ACTH in the Treatment of Sympathetic Ophthalmia, Acta ophth. **29**:239, 1951. (*m*) Haik, G. M.; Waugh, R. L., Jr., and Lyda, W.: Sympathetic Ophthalmia, A. M. A. Arch. Ophth. **47**:437, 1952. (*n*) Lavery, F. S.; Werner, L. E.; O'Donoghue, S.; Guinan, P. M., and MacDougald, J.: Use of Cortisone in Diseases of the Eye, Brit. M. J. **1**:1285, 1951. (*o*) Barrious, R. R., and Barrière, R. B.: Cortisone in Ophthalmology, Arch. Soc. oftal. hispano-am. **11**:276, 1951. (*p*) McLean, J. M.; Gordon, D. M., and Koteen, H.: Clinical Experience with ACTH and

remarkable ability of the hormonal agents is not absolute. Hormonal therapy is of greatest effectiveness in ocular diseases which are the result of acute trauma—allergic, toxic, or physical—and those in which the histologic changes incident to

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99. (*a*) Lavat: Cortisone in the Treatment of Phlyctenular Keratoconjunctivitis, Semana méd. **27**:1000, 1951. (*b*) Horne, G. O.: Topical Treatment of Cortisone in Syphilitic Ocular Disease, Brit. M. J. **2**:1289, 1951. (*c*) Lavery, F. S.; Werner, L. E., and O'Donoghue, D.: Use of Cortisone in Diseases of Eye, ibid. **2**:1285, 1951. (*d*) Thygeson, P.: Etiology and Treatment of Phlyctenular Keratoconjunctivitis, Am. J. Ophth. **34**:1217, 1951. (*e*) Siltzbach, L. E.: Effect of Cortisone in Sarcoidosis, Am. J. Med. **12**:139, 1952. (*f*) Gindel, B. R.; Young, J. M., and Greiner, D. J.: Sarcoidosis, ibid. **12**:205, 1952. (*g*) Siltzbach, L. E.; Posner, A., and Medine, M. M.: Cortisone Therapy in Sarcoidosis, J. A. M. A. **147**:927, 1951. (*h*) Small, M. J.: Favorable Response of Sarcoidosis to Cortisone Treatment, ibid. **147**:932, 1951. (*i*) Lovelock, F. J., and Stone, D. J.: Cortisone Therapy of Boeck's Sarcoid, ibid. **147**:930, 1951. (*j*) Small, M. J.: Pulmonary Sarcoidosis, ibid. **147**:932, 1951. (*k*) Kierland, R. R.; O'Leary, P. A.; Brunsting, L. A., and Didcoct, J. W.: Cortisone and Corticotropin (ACTH) in Dermatology, ibid. **148**:23, 1952. (*l*) Maddin, S., and Danto, J. L.: Results of Topical Application of Cortisone in Congenital Syphilitic Interstitial Keratitis, A. M. A. Arch. Dermat. & Syph. **64**:437, 1951. (*m*) Freedlander, A. S.: Observations on Use of ACTH and Cortisone in Treatment of Asthma, Hay Fever and Other Allergic Conditions, Ann. Allergy **9**:588, 1951. (*n*) Sharnoff, J. G.; Carideo, H. L., and Stein, I. D.: Cortisone-Treated Scleroderma: Report of a Case with Autopsy Findings, J. A. M. A. **145**:1230, 1951. (*o*) Ormsby, H. L.; Shirley, B. Y.; Aikenhead, J. F., and Murray, R. G.: ACTH and Cortisone in Eye Disease, Canad. M. A. J. **66**:62, 1952. (*p*) Beerman, H.; Ford, W. T.; Nicholas, L., and Katzenstein, L.: Syphilis, A. M. A. Arch. Int. Med. **89**:309; 464, 1952. (*q*) Cortisone in Interstitial Keratitis, Editorial, Am. J. Syph. **35**:88, 1951. (*r*) Vesterdal, E.: ACTH in the Treatment of Sympathetic Ophthalmia, Acta ophth. **29**:239, 1951; (*s*) Acute Fibrinous Iridocyklitis, ibid. **29**:509, 1951. (*t*) Lawrence, H. G., Jr.: Value of ACTH and Cortisone in Ocular Inflammations, South. M. J. **45**:65, 1952. (*u*) Crawford, H. E.: Cortisone in Secondary Glaucoma, Am. J. Ophth. **34**:1320, 1951. (*v*) Mundy, M. L.; Howard, R. M.; Stillman, P. H., and Bevans, M.: Cortisone Therapy in a Case of Rheumatoid Nodules of the Eye in Chronic Rheumatoid Arthritis, A. M. A. Arch. Ophth. **45**:531, 1951. (*w*) Kellerman, L.: Pregnenolone Therapy in Uveitis, ibid. **46**:419, 1951. (*x*) Thiel, R.: Cortisone Therapy in Eye Disease, Klin. Monatsbl. Augenh. **119**:161, 1951. (*y*) Schwarz, F.: Cortisone Therapy in Ophthalmic Disease, Kresge Eye Inst. Bull. **2**:59, 1951. (*z*) Arruga, H.: Cortisone in Ophthalmology, Arch. Soc. oftal. hispano-am. **11**:585, 1951. (*a'*) Perera, C. A., and McLean, J.: Use of ACTH and Cortisone, A. M. A. Arch. Ophth. **46**:105, 1951.

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(Footnotes continued on next page)

the ocular disease are primarily those of edema and cellular infiltration, and in which tissue destruction and secondary granulomatous changes have not taken place previous to the institution of therapy. Recurrence is common when administration

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of therapy is discontinued. In such conditions as secondary glaucoma, optic neuritis, interstitial keratitis, and early clouding of the corneal graft the results with these agents are not consistently effective. In hemorrhagic disorders, such as Coats's disease, Eales's disease, diabetic retinopathy, and malignant exophthalmos, no clear-cut therapeutic effect has as yet been demonstrated, although there are favorable reports in early cases. In the vast majority of ocular degenerations these agents are without effect. The tables prepared for the 1951 review showing the effectiveness of these agents are, in large measure, still applicable. Most important of the conditions benefited are those of acute nongranulomatous uveitis, allergic keratitis, vernal conjunctivitis, very early interstitial keratitis, and early sympathetic ophthalmia. These are largely self-limiting diseases. If hormonal therapy is maintained over the course of the active phase of the disease, the inflammation and exudation will be controlled; then, as the disease runs its course, the eye will quiet and remain quiet. As stressed by Woods and others, hormonal therapy does not affect the causal disease, but, rather, influences the reaction of the tissues to the causal irritant. It is generally agreed throughout the ophthalmologic literature, as well as the general literature, that in acute bacterial infections hormonal therapy should be accompanied by specific antibiotic treatment for elimination of the infection.

The dosage schedules suggested in last year's review are still applicable. Topical administration of cortisone or "hydrocortisone" is preferred for inflammations of the anterior ocular segment. For disease of the posterior segment systemic administra-

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Cortisone on Development and Progress of Pigmented Nevi, J. A. M. A. **147**:941, 1951. (*k*) Bottino, C.: The Blood-Aqueous Barrier and Luminous Stimuli, Ann. ottal. e clin. ocul. **77**: 281, 1951. (*l*) Ashton, N., and Cook, C.: Effect of Cortisone on Healing of Corneal Wounds Brit. J. Ophth. **35**:708, 1951. (*m*) Ashton, N.; Cook, C., and Langhan, M.: Effect of Cortisone on Vascularization and Opacification of Cornea Induced by Alloxan, ibid. **35**:718, 1951. (*n*) Lister, A., and Greaves, D. P.: Effect of Cortisone on the Vascularization Which Follows Corneal Burns, ibid. **35**:725, 1951. (*o*) Cook, C., and MacDonald, R. K.: Effect of Cortisone on the Permeability of the Blood-Aqueous Barrier to Fluorescein, ibid. **35**:730, 1951. (*p*) Steen, A. S.: Effect of Cortisone on Tissue Cultures, ibid. Ophth. **35**:741, 1951. (*q*) von Sallmann, N. L.; Jones, I. S.; Wiggins, R. L., and Lokulosa, E. D.: Influence of Cortisone on Wound Healing, Macrophagocytosis, and Capillary Permeability, Wien. klin. Wchnschr. **63**:684, 1951. (*r*) Leopold, I. H.; Purnell, J. E.; Cannon, E. J.; Steinmetz, C. G., and McDonald, P. R.: Local Cortisone in Ophthalmology, Am. J. Ophth. **34**:361, 1951. (*s*) Fritz, A.: Study of the Effects of Cortisone on the Capillary Stream of the Eye, Bull. Soc. opht. France **2**:153, 1951. (*t*) Cordier, D.; Cordier, G., and Bavoux, M.: Changes in the Potassium Content of Aqueous Humor Caused by Experimental Traumatic Shock, Experientia **6**:345, 1951. (*u*) Lepri, G., and Montanari, L.: Action of Corticotropic Hormone, ACTH, of Desoxycorticosterone Acetate, and of Adrenal Cortex Extract on Contents of Hyaluronidase in the Aqueous Humor, Arch. ottal. **55**:329, 1951. (*v*) Simonelli, M., and Calamandrei, G.: Behavior of the Blood-Aqueous Barrier After the Administration of ACTH, Gior. ital. oftal. **4**:340, 1951. (*w*) Tarantino, C.: Presence of ACTH in the Placenta, Folia endocrinol. **4**:197, 1951. (*x*) Opsahl, Long, and Fry.[65e] (*y*) Opsahl, J. C., and Long, C. N. H.: Identification of ACTH in Human Placental Tissue, ibid. **24**:199, 1952. (*z*) Pelloja, M.: Role of Pituitary and Adrenal Glands in Inhibition of Hyaluronidase by Salicylates in Vivo, Lancet **1**:733, 1952. (*a'*) Little, H. O.: Cortisone in a Perforating Eye Wound, Brit. J. Ophth. **35**:790, 1951.

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tion of corticotropin or cortisone is desirable. In resistant cases the intravenous use of corticotropin, up to 40 mg. daily, may be indicated. However, with this route of administration, one should rarely exceed 15 to 20 mg. in a shorter period than six or seven hours. Cortisone and "hydrocortisone" can be administered topically in the form of an ointment or a solution or by subconjunctival injection. As noted by McDonald, Leopold, Vogel, and Mulberger,[50b] subconjunctival injections of Compound F, or "hydrocortisone," remain in the tissues for a much greater period than Compound E, or cortisone. For diseases of the external eye and anterior ocular segment, corneal diseases, scleritis, episcleritis, and anterior uveitis, local therapy is equal, if not superior, to parenteral administration. It is also free from the dangers of undesired physiologic effect, permits indefinite administration without danger to the patient, and is relatively inexpensive. Particular attention should be paid to the observation of the greater beneficial effect from local use of hydrocortisone than from local use of cortisone in the therapy of vernal conjunctivitis.[50b]

The results with sarcoidosis in the literature of the past year have been rather favorable.[99e-j] However, in most of the granulomatous forms of uveitis the actions of these hormones are not so spectacular; and, of course, it is unnecessary to mention that in ocular tuberculosis one should use these agents guardedly. Kellerman's observations with pregnenolone failed to show any beneficial effect for this hormone in uveitis.[99w] It may be of interest to note a single case of temporal arteritis in which corticotropin therapy was beneficial.[100n] In the hands of several investigators,[100s-v] experimental herpes simplex keratitis failed to respond to cortisone administered intramuscularly, subconjunctivally, or topically. This suggests that hypersensitivity does not play an important role in the early stages of this disease. However, cortisone will reduce corneal vascularization even in this condition.[100v]

Intermedin, corticotropin, and cortisone have been found to produce a definite improvement, not only in visual acuity and visual fields but in dark adaptation, in patients with retinitis pigmentosa, according to Steffensen and Kukora[100y] and Gordon and associates.[101a] Steffensen and Kukora[100y] believed that intermedin, which was present as a contaminant in corticotropin, did not appear to account for the apparently favorable effect that corticotropin had in some cases of retinitis pigmentosa, although intermedin had a definite beneficial effect. It is interesting that Johnsson and Högberg[100x] found that intermedin and active adrenocorticotropic-hormone peptide are closely related or identical.

There are numerous references showing the improvement following the local use of cortisone in congenital syphilitic interstitial keratitis. However, a word of caution must be said, for it has been seen in many instances that, although the condition quiets, when therapy has stopped it flares again, whereas before the advent of cortisone the treatment of interstitial keratitis was usually followed by a quiet eye for the remainder of the patient's life, once the severe attack had subsided. Now we are seeing recurrent lesions which continue, although each attack is treated and quieted with cortisone. It may be that the patient is not forming a sufficient number of antibodies to handle the reaction. It may be that cortisone or corticotropin is blocking the natural processes of resistance.[103]

103. Simpson and others.[101e] Woods.[98a] Pinkerton.[98a'] Horne.[99b] Kierland and others.[99k] Maddin and Danto.[99l] Beerman and others.[99p] Crawford.[99u]

The majority of reports concerning sympathetic ophthalmia have been favorable.[104]

Favorable results have been reported with the use of these agents in myasthenia gravis. In most patients neostigmine was still necessary, but the requirements were lowered.[105] The mechanism of action and the therapeutic value of corticotropin and cortisone in myasthenia gravis are still uncertain and require more study.[101b,c] It has been suggested by Torda and Wolff [101c] that corticotropin has a specific effect on the mechanism responsible for the symptoms of myasthenia gravis by increasing the synthesis of acetlycholine and by restoring to normal the impaired ability to maintain the amplitude of the action potential during repetitive stimulation. The effect of corticotropin on the nerve is due, according to their suggestion, to an indirect mechanism involving an increase in the intracellular concentration of substances that augment the activity of choline acetylase.

Moutinho [100k] suggests that the improvement in patients with multiple sclerosis following exploration of the sinuses may be due to the shock produced as the result of the operation, thus liberating corticoid materials.

Experimental Observations.[101]—The mechanism of the therapeutic action of cortisone and corticotropin in ocular disease is still undetermined. However, experimental studies on ocular tissues have revealed the same changes as those described previously for other body tissues.

Cortisone blocks inflammatory reaction due to various toxic agents.[106] These agents reduce corneal vascularization.[107] Corticotropin and cortisone increase local pigmentation.[101j] These agents fail to disturb the permeability of the blood-aqueous barrier in the normal eye but may decrease the permeability in the inflamed eye.[108] There is considerable evidence that these agents interfere with ocular wound healing, particularly of the mesenchymal elements.[109] The observation that these agents interfere with the action of hyaluronidase has been confirmed in ocular tissues by Lepri and Montanari.[101u] These authors demonstrated that corticotropin produces a visible diminution of the hyaluronidase content of the aqueous after one injection and a more pronounced effect after prolonged treatment. Cortisone had less effect in this regard, and desoxycorticosterone showed no action whatsoever.[101w-z] Through this hyaluronidase-inhibitory action of cortisone and corticotropin, it has been possible to demonstrate that placental tissue possesses these hormones. In view of the vast amount of literature on the value of tissue therapy, this observation would seem to be very striking and important for the studies of Opsahl and associates,[101y] in particular, indicate that placental extracts contain considerable adrenocorticotropic activity.[101w-z]

Since there seems to be a relation between the severe type of exophthalmos, especially of the post-thyroidectomy type, and sex, in that it occurs more frequently in males than in females, the statistics strongly suggest a relation of the sex steroid hormones to exophthalmos. Smelser and Ozanics [101g] induced exophthalmos by injection of anterior pituitary extract into thyroidec-

104. Woods.[98a] Berens and Girard.[98e] McLean.[98f] Hill, Dennis, and Shannon.[98g] Paich-Szanto.[98j] Laws and Howard.[98k] Vesterdal.[98l] Duke-Elder and others.[98w] Perera and McLean.[99a'] Schwarz.[99y] Arruga.[99z] Meiffret.[100j] Agatston.[100x]

105. Millikan and Eaton.[101b] Torda and Wolff.[101c]

106. Bottino.[101k] Bourquin.[101l] Selye.[82] von Sallmann and others.[101q] Leopold and others.[101r] Fritz.[101s] Wood.[102a]

107. Wood.[102a] Fritz.[101h] Ashten, Cook and Langhan.[101m] Lister and Greaves.[101n] von Sallmann and others.[101q] Leopold and others.[101r] Fritz.[101s]

108. Cook and MacDonald.[101o] von Sallmann and others.[101q] Leopold and others.[101r] Fritz.[101s] Simonelli and Calamandrei.[101v] Wood.[102a]

109. Wood.[102a] Ashton and Cook.[101l] Steen.[101p] von Sallmann and others.[101q] Leopold and others.[101r]

tomized guinea pigs and found that the production of such exophthalmos was not affected by the absence of gonads or by an excess of androgens administered parenterally. Injection of adrenal cortex extract, desoxycorticosterone, and cortisone had no effect on the orbital tissue of controls and of animals with exophthalmos and did not influence the degree of exophthalmos. In the female guinea pig, the administration of large amounts of estradiol did appear to reduce the exophthalmos. This also occurred in the normal eye and orbit. Although estradiol affects the orbital tissues, directly decreasing their mass, it did not prevent them from reacting to injected anterior pituitary hormone to some extent. In this way estradiol acted similarly to thyroxin.

Parenteral injection of cortisone hastens the absorption of autogenous red blood corpuscles injected into the vitreous of rats. Increased macrophagocytosis is probably responsible for this phenomenon. The permeability of the blood-aqueous barrier for fluorescein seemed to be slightly less in cortisone-treated rabbits than in normal animals.[101q] Simonelli and Calamandrei[101r] found, however, that parenteral administration of a daily dose of 30 to 45 mg. of corticotropin for six to eight days produced no variation in the permeability of the blood-aqueous barrier in normal subjects. The determinations were made by the Amsler-Huber fluorescein test. There is evidence also that experimental traumatic shock fails to influence the permeability of the blood-aqueous barrier.

It has been demonstrated that antibodies which have been formed after injection of corticotropin are not really true antihormones, but are probably antibodies against an impurity contained in the preparation.[102b]

AUTONOMIC DRUGS

An understanding of the classification of the autonomic drugs at the present time is best obtained by a knowledge of the neurohumoral theory of nerve-impulse transmission. Using this theory, Leopold[110] has prepared a classification of the drugs used in ophthalmology (Table 2; Fig. 2).

Acetylcholine.—This neurohormone, which is well known to be the one responsible for activation at the ending of parasympathetic nerve fibers, at the sympathetic and parasympathetic ganglian throughout the body, and at the ending of nerves supplying skeletal muscle, may be decreased by the action of procaine or by botulinum toxin, as reported by Bergel.[111] It is doubtful whether the quantity of acetylcholine can be directly increased by any substance, but it can be increased indirectly by anticholinesterase compounds. Mazzella and Minz[112] have produced evidence that acetylcholine in the aqueous humor does not rise in concentration as the result of contraction of the iris muscle, but diffuses into the blood, for they found no alteration in concentration after the use of anesthetic, on exposure of the eye to light or dark, whatever the intensity of the light, on removal of the superior cervical ganglion, or on intravenous injection of atropine. McLennan and Elliott[113] indicate that adenosinetriphosphate is important in the synthesis of acetylcholine. Several investigators have attempted to create other compounds with chemical structures similar to acetylcholine which would mimic acetylcholine in its action.[114]

Adrenergic-Nerve Mediator.—Von Euler has reviewed the evidence that arterenol (norepinephrine) is the substance liberated at the ending of the sympathetic nerves. The possible adrenergic-nerve mediators[115] are arterenol, epinephrine, tyramine, and hydroxytyramine. The

110. Leopold, I. H.: Autonomic Drugs: Their Influence on Choroidal Vessel Calber, Tr. Am. Ophth. Soc. **49**:625, 1951.

111. Bergel, F.: Parasympathomimetics and Anticholinesterases, J. Pharm. & Pharmacol. **3**:385, 1951.

112. Mazzella, H., and Minz, B.: Acetylcholine in the Aqueous Humor of the Rabbit Eye, Compt. rend. Soc. biol. **145**:632, 1951.

113. McLennan, H., and Elliott, K. A. C.: Adenosine Diphosphate Concentration and the Synthesis of Acetylcholine by Brain Preparation, Arch. Biochem. **36**:89, 1952.

114. Ing, H. R.; Kordick, P., and Tudor Williams, D. P. H.: Studies on the Structure Action Relationships of the Choline Group, Brit. J. Pharmacol. **7**:103, 1952.

115. von Euler, U. S.: The Nature of Adrenergic Nerve Mediators, Pharmacol. Rev. **3**:247, 1951; Arterenol-Adrenomedullary Hormone and Chemical Transmitter of Adrenergic Nerves, Ergebn. Physiol. **46**:261, 1950.

TABLE 2.—*Classification of Autonomic Drugs*

I. DRUGS ACTING ON PARASYMPATHETIC SYSTEM (PARASYMPATHOMIMETIC)

A. Drugs acting on effector cells so as to mimic action of acetylcholine, or the so-called neurohumoral transmitter

1. Pilocarpine
2. Carbachol U. S. P. (doryl®)
3. Furtrethenium iodide (furmethide® iodide)
4. Methacholine chloride U. S. P. (mecholyl® chloride)

B. Inhibitors of enzyme cholinesterase, which normally hydrolyzes neurohumoral transmitting agent, acetylcholine (the action of the locally produced acetylcholine is therefore markedly prolonged)

1. Physostigmine—tertiary compound with a urethan group
2. Neostigmine (prostigmin®)—quaternary compound with a urethan group
3. Diisopropyl fluorophosphate
4. Tetraethylpyrophosphate
5. Hexaethyltetraphosphate

C. Drugs producing varying degrees of paralysis of effector cells to impulses from parasympathetic postganglionic nerves or to stimulation by drugs like pilocarpine. (These paralyzing drugs prevent access of acetylcholine or stimulating drug to the irritable patches of the surface of effector cells)

Visceral and Intraocular Structures

1. Atropine
2. Homatropine
3. Eucatropine U. S. P. (euphthaline®)
4. Scopolamine
5. Hyoscyamine ("Duboisine")
6. Dibutoline
7. Banthine®

Skeletal Muscle

1. Curare
2. Tubocurarine chloride
3. Decamethonium iodide

II. DRUGS ACTING AS SYMPATHOMIMETIC AGENTS

A. Drugs acting on effector cells so as to mimic action of the neurohumoral transmitter, probably epinephrine, sympathin E, or arterenol

1. Epinephrine
2. Phenylephrine (neo-synephrine®) hydrochloride
3. Hydroxyamphetamine (paredrine®)
4. Ephedrine
5. Amphetamine (benzedrine®)

} Phenylalkylamine derivatives

B. Enzyme inhibitors preventing destruction of epinephrine, which is essential for neurohumoral transmission in the sympathetic nerve endings (The locally produced epinephrine thus has a prolonged effect. This antiepinephrine substance may be an amine oxidase)

1. Cocaine (?)
2. Ephedrine (?)
3. Amphetamine (?)
4. Procaine (?)

C. Adrenergic-Blocking Agents—compounds that specifically inhibit certain responses of effector cells to epinephrine, related amines, and sympathetic-nerve impulses.

1. Beta-halo-alkylamines, e. g., dibenamine® (N-N-dibenzyl-β-chloroethylamine hydrochloride)
2. Imidazolines, e. g., benzazoline (priscol®)
3. Benzodioxanes, e. g., 933 F
4. Ergot alkaloids, e. g., dihydroergocornine
5. Yohimbines

III. GANGLION-BLOCKING AGENTS

Agents interfering with transmission through ganglia, similar to secondary effects (paralyzing) of nicotine (large doses)

1. Tetraethylammonium chloride (etamon® chloride)
2. Pentamethonium iodide (C_5)
3. Hexamethonium iodide (C_6)

IV. CENTRALLY ACTING AGENTS

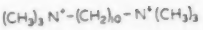
Drug influencing centers in brain, e. g., medulla and diencephalon, that are superimposed over the connector cells of the autonomic system

1. Hypothalamic center responds to cholinergic agents, e. g., acetylcholine; physostigmine, etc., can produce parasympathetic or sympathetic activity, depending on area of hypothalamus stimulated; e. g., stimulation of preoptic region gives parasympathetic response; postchiasmal area, sympathetic response
2. Cerebral cortex also responds to acetylcholine and physostigmine
3. Other agents or conditions that act centrally are morphine, CO_2 and oxygen lack

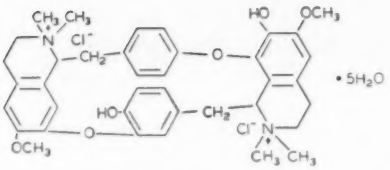
V. DIRECT ACTING AGENTS

1. Histamine
2. Barium, potassium, etc.
3. Procaine (?)
4. Ergot alkaloids, benzodioxanes

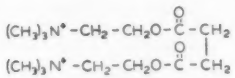
NEUROMUSCULAR BLOCKING AGENTS



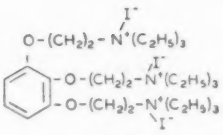
Decamethonium (C-10)



Tubocurarine, U.S.P. Chloride

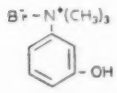


Succinylcholine



Flaxedil ® Gallamine triiodide

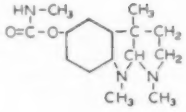
ANTICURARE AGENT



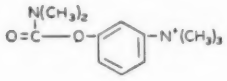
3-Hydroxyphenyltrimethyl-ammonium bromide

ANTICHOLINESTERASE AGENTS

I. Reversible



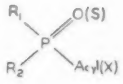
Physostigmine, U.S.P.

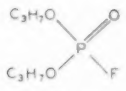


Neostigmine, U.S.P.

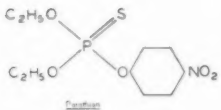
II. Irreversible

General Formula (Gerhard Schrader)

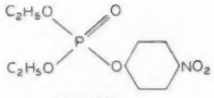




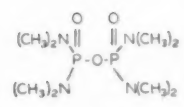
Isopropyl Fluorophosphate



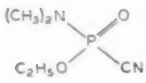
Parathion



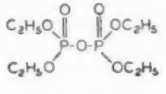
Mintacol (E600)



Tetraethylpyrophosphate



Tabun



Octomethylpyrophosphoramide

Figure *2A* and *2B*

last two substances have a weak sympathomimetic action. If the term sympathin is to continue in use, it should be defined as the group of substances liberated on adrenergio-nerve stimulation. The differences in the actions of epinephrine and arterenol are included in Figure 3, modified from data presented by von Euler.[115] The sympathomimetic activity of aqueous humor is definitely increased after stimulation of the cervical sympathetic nerve, but the relative amounts of epinephrine and arterenol in the aqueous vary. Epinephrine usually predominates in the aqueous humor. Epinephrine is a more potent iris dilator.[116]

West has demonstrated that arterenol has a depressant action in the normal animal and that epinephrine may under certain circumstances sensitize the nictitating membrane and nonpregnant

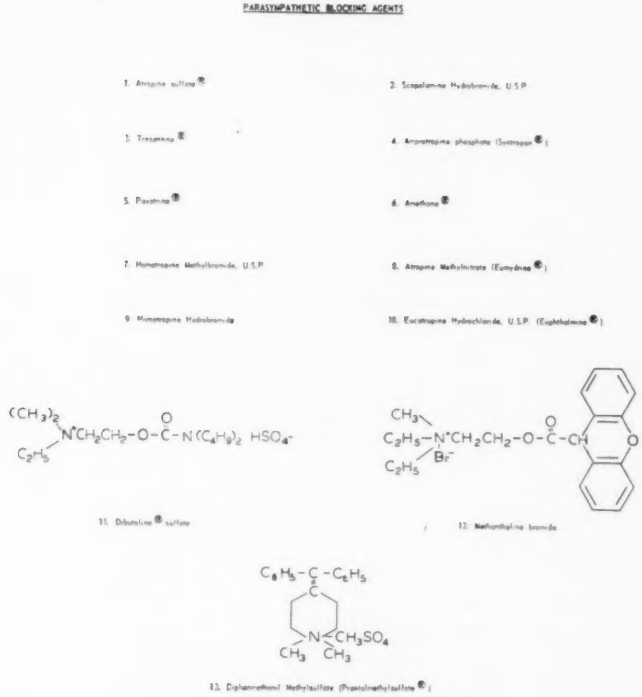


Fig. 2.—Structural formulas of autonomic drugs.

uterus of a spinal cat to arterenol.[117] These substances can be differentiated by paper chromatography.[118] West has also demonstrated that methylene blue can potentiate the action of arterenol.[118]

116. Wakim, K. G., and Essex, H. E.: Comparison of the Circulatory Effects of Epinephrine and Norepinephrine, Circulatation **5**:370, 1952.

117. West, G. B.: Nor-Adrenalin: A Depressor Action in the Normal Animal, J. Pharm. & Pharmacol. **3**:340, 1951; Can Adrenaline Potentiate the Action of Noradrenaline? ibid. **3**:571, 1951; Analysis of Pharmacopoeial Samples of Adrenaline, a Limit Test for Noradrenaline in Adrenaline, ibid. **4**:95, 1952.

118. West, G. B.: Some Actions of Methylene Blue and of Mepyramine in the Body, J. Pharm. & Pharmacol. **3**:656, 1951.

Cholinesterase.—It has become evident from considerable enzymological work that there are two main types of cholinesterase. One of them, the acetylcholines-

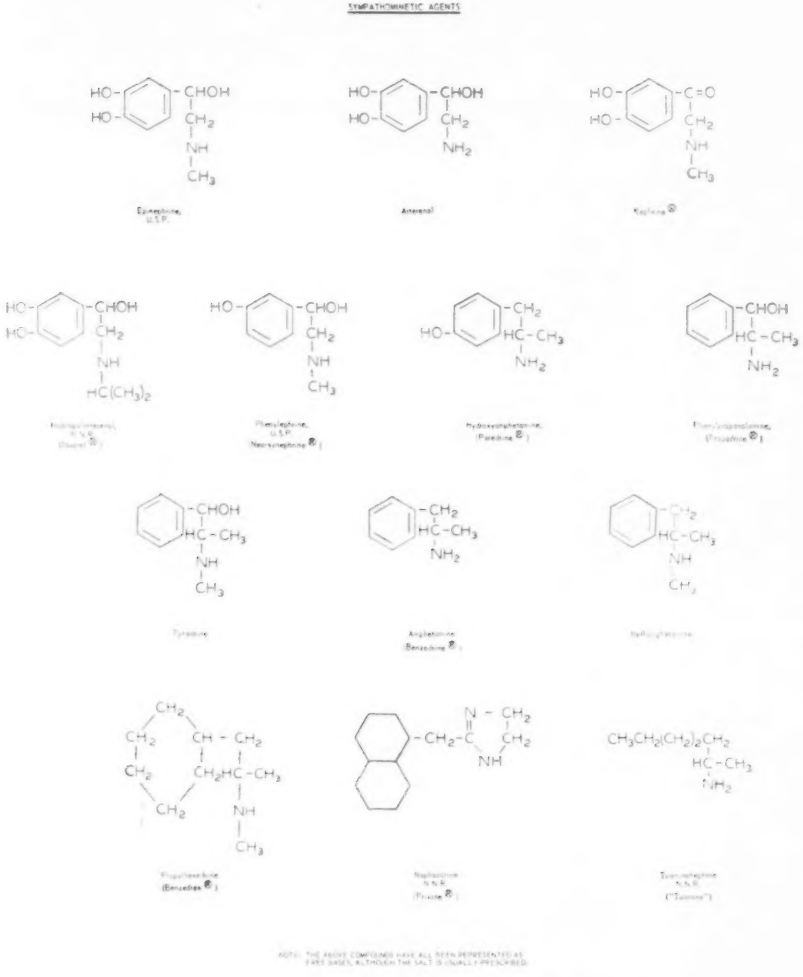
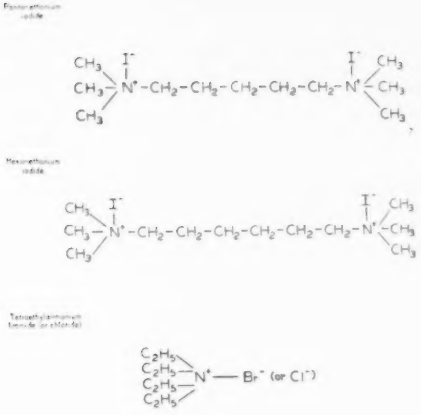


Figure 2

terase, or specific cholinesterase, or true cholinesterase, is present in high concentrations in all nerve tissues and human erythrocytes and hydrolyzes acetylcholine rapidly. The other cholinesterase, known also as nonspecific cholinesterase, or

GANGLION BLOCKING AGENTS



ADRENERGIC BLOCKING AGENTS

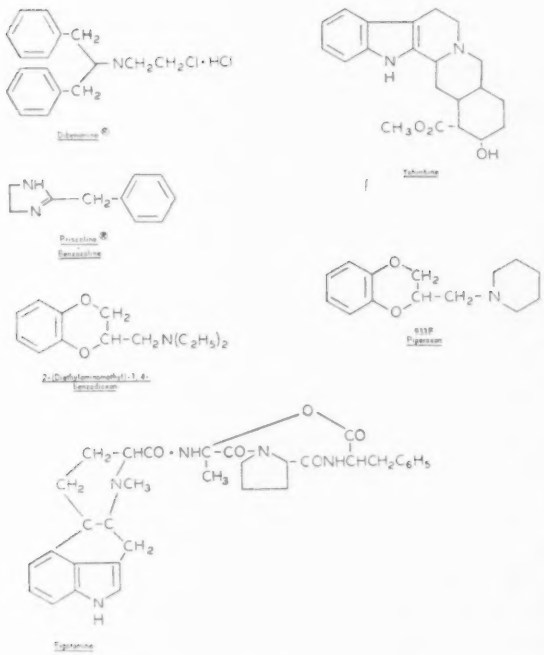


Figure 2

pseudocholinesterase, splits longer-chain choline esters at a greater velocity than does acetylcholine.[119]

Among the great variety of compounds known to inhibit acetylcholinesterase and nonspecific cholinesterase, three groups may be distinguished: (1) quaternary ammonium bases (neostigmine, methylene blue); (2) physostigmine and other urethans, and (3) organophosphorus compounds. These inhibitors may be classified by virtue of their length of action into those which reversibly inhibit cholinesterase and the irreversible inactivators.[119] Physostigmine and neostigmine are examples of reversible inhibition; diisopropyl fluorophosphate, of irreversible inac-

	ARTERENOL	EPINEPHRINE
Iris	Weak dilator	Potent dilator
Coronary	Dilates	Less potent
Vessels	Constriction	Less potent
Mean blood pressure	Elevates	Less effective
Minute volume	No effect	Increases
O_2 consumption	Slight increase	Marked increase
Enhancing of acetylcholine effect on sympathetic ganglion	Slight	Marked
Anxiety feeling	None	Definite
Aqueous humor concentration	Small	Predominates

Fig. 3.—Comparison of actions of sympathetic neurohormones.

tion. The general formulas of these compounds are included in Figure 2. The general formula for anticholinesterase agents is based on the work of Schrader.[120]

Holmstedt[119b] has found that "tabun" (dimethylamidoethoxyphosphoryl cyanide) and its homologues act like other alkyl phosphates, mainly by virtue of their cholinesterase-inhibiting activity. "Tabun," however, had less central effect than diisopropyl fluorophosphate.

119. (*a*) Leopold.[119] (*b*) Holmstedt, B.: Synthesis and Pharmacology of Dimethylamidoethoxy-Phosphoryl Cyanide (Tabun), Acta physiol. scandinav. (Supp. 90) **25**:11, 1951.

120. Schrader, G.: Development of New Insecticides on the Basis of Organic Fluorene and Phosphorus Compounds, Weinheim, Monographie zu Agnew Chemie, no. 62, 1951.

Because of the widespread use of these organic phosphate anticholinesterase inhibitors as insecticides, many instances of poisoning have been reported and studied.[121] The usual form of therapy is the use of a parasympathomimetic blocking agent, such as atropine.[122]

Studies of the specific cholinesterases in the rabbit, horse, and man have shown that the specific and nonspecific cholinesterases in the superior cervical ganglion are similar to those which have been described in the intestine, and that there is a difference in the cholinesterase of the horse and that of man, particularly in respect to its inhibition by procaine.[123]

The increased sensitivity to applied acetylcholine of effector organs deprived of their cholinergic innervation has often been attributed to a decrease in the enzyme cholinesterase in these tissues. Brooks and Myers [124] were unable to demonstrate any change in content of true cholinesterase in most denervated muscle tissue studied. This would tend to rule out this theory of sensitization after denervation as being due to a decrease in the enzyme cholinesterase.

Additional evidence has been presented that the nonspecific cholinesterase is not essential to normal ganglionic transmission, whereas inhibition of specific cholinesterase beyond 50% produces increasing effects on transmission which are probably attributable to the enzymatic inhibition.[125]

It has been shown by many workers that acetylcholine and cholinesterase are important in the transmission mechanism and function of the central nervous system.[126]

Hutchinson and Widdowson [127] have measured the serum cholinesterase in healthy British children and found it to be approximately the same as, or a trifle higher than, that in healthy adults. In human cord blood it amounts to approximately 50 units per 100 cc. In the first three weeks of life this increases steadily to 85 units. In the healthy children measured by Hutchinson it was 100 units, and in the average adult it is about 75 to 80 units per 100 cc.

Vorhaus [128] found no change in serum cholinesterase values in patients with myasthenia gravis, asthma, hyperthyroidism, or hypertension. His data suggest that the cholinesterase of serum is synthesized with the albumin molecule. Its synthesis is stimulated by factors that stimulate albumin production. Depression of serum cholinesterase followed administration of tetraethylammonium, vitamin K, folic acid, and amobarbital sodium (amytal® sodium).

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121. Hamblen, D. O., and Marchand, J. F.: Phosphate Ester Poisoning: A New Problem for the Internist, Ann. Int. Med. **36**:50, 1952. Douglas, W. W., and Matthews, P. B. C.: Acute Tetraethylpyrophosphate Poisoning in Cats and Its Modification by Atropine or Hyoscine, J. Physiol. **116**:202, 1952. Callaway, J.; Davies, D. R., and Rutland, J. P.: Blood Cholinesterase Levels and Range of Personal Variation in a Healthy Adult Population, Brit. M. J. **2**:812, 1951. Barnes, J. M., and Davies, D. R.: Blood Cholinesterase Levels in Workers Exposed to Organo-Phosphorus Insecticides, ibid. **2**:816, 1951.

122. Dickens, P. F., Jr.; Rizzolo, J., and Bayliss, M. W.: Treatment of Nerve Gas Casualties, U. S. Armed Forces M. J. **2**:1609, 1951. Mouter, L. A.: Specificity of Cobra Venom Cholinesterase, Biochem. J. **50**:122, 1951. Reder, J. A.; Ellenwood, L. E., and Coon, J. M.: Tolerance to Octamethyl Pyrophosphoramide, Federation Proc. **11**:386, 1952.

123. Koelle, G.: Types and Distributions of Cholinesterases in the Rabbit, Federation Proc. **11**:363, 1952. Whittaker, V. P.: Specificity Mode of Action and Distribution of CHE, Physiol. Rev. **31**:312, 1951. Kalow, W.: A Comparison of the Serum Cholinesterases of Man and Horse, Federation Proc. **11**:360, 1952.

124. Brooks, V. B., and Myers, D. K.: Cholinesterase Content of Normal and Denervated Skeletal Muscle in the Guinea-Pig, J. Physiol. **116**:158, 1952.

125. Kamijo, K., and Koelle, G. B.: Relationship Between Cholinesterase Inhibition and Ganglionic Transmission in the Cat, Federation Proc. **11**:360, 1952.

126. Duke, H. N.; Pickford, M., and Watt, J. A.: The Immediate and Delayed Effect of DFP Injected into the Supraoptic Nuclei of Dogs, J. Physiol. **111**:81, 1950. Greig, M. E., and Mayberry, T. C.: Relationship Between Cholinesterase Activity and Brain Permeability, J. Pharmacol. & Exper. Therap. **102**:1, 1951.

127. Hutchinson, A. O., and Widdowson, E. M.: Cholinesterase Activities in the Serum of Healthy British Children, Nature, London, **169**:284, 1952.

128. Vorhaus, L. J.: Serum Cholinesterase in Health and Disease, Am. J. Med. **12**:112, 1952.

DeRoetth [129] studied the cholinesterase in the ocular tissues following various physiologic and pathologic changes and demonstrated that there was an excess of cholinesterase in the iris and ciliary body of the rabbit. Only about 15% of the total amount is necessary for normal pupillary function. He also showed that after retrobulbar injection there is a loss of cholinesterase

Fig. 4.—Chemical relations of acetylcholine and other quaternary ammonium compounds.

activity. It actually drops to 40% of normal and remains there for several weeks. This is probably due to degeneration of the parasympathetic nerve fibers in these tissues, and this, in

129. DeRoetth, A., Jr.: Further Studies on Cholinesterase Activity in Ocular Tissues, Am. J. Ophth. **34**:120, 1951.

turn, has been caused by the paralytic action of alcohol in the ciliary ganglion. The remaining enzyme activity can be attributed mainly to the cholinesterase in the postsynaptic membrane. Ciliary ganglionectomy was also followed by a decrease in the cholinesterase content to approximately 40% of normal, showing the similarity between retrobulbar alcohol injection and ganglionectomy.

Adrenergic-Blocking Agents.—The formulas of several of these adrenergic-blocking agents are listed in Figure 2. The studies on these agents have proceeded during the past year. They are reported to be useful in cases of glaucoma in which the condition has not responded to other tension-lowering medication.

Ganglion-Blocking Agents.—The striking pharmacologic action of methonium compounds is now well known, especially the blocking of neuromuscular trans-

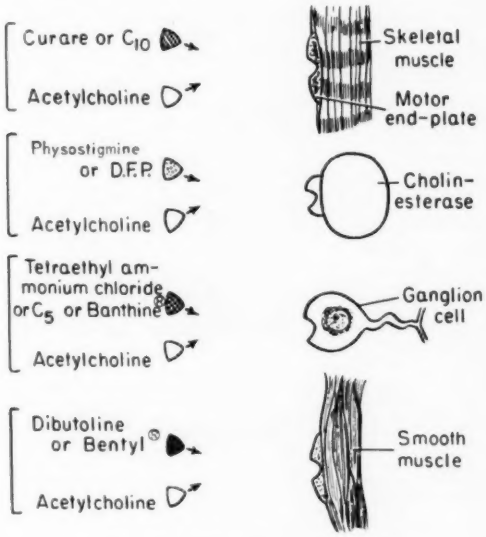

Fig. 5.—Substrate competition.

mission by decamethonium, which leads to muscular paralysis, and the blocking of ganglionic transmission by pentamethonium, which produces, among other effects, a well-marked fall in blood pressure.

These agents do not depress all autonomic ganglia equally. Animal experiments indicate that the parasympathetic ganglia in the salivary gland are the most sensitive. Then follow, in order of sensitivity, the superior cervical ganglion, the vasomotor ganglia, the visceral ganglia, and, finally, the vagal ganglon with fibers to the heart. There are also minor differences in selective ganglionic depression among the methonium compounds containing four, five, or six CH_2 groups. Tetraethylammonium differs from hexamethonium in causing a much greater paralysis of the ciliary muscle when equihypotensive doses of the two drugs are given. It is possible, therefore, that more specific ganglion-blocking compounds may yet be discovered.[130]

130. Keele, C. A.: The Actions of Methonium Compounds with Special Reference to Paralysis of Autonomic Ganglia, Arch. Middlesex Hosp. **2**:23, 1952.

Because of a structural relationship to acetylcholine, many quarternary ammonium compounds are pharmacologically active at cholinergic synapses and neuroeffector junctions. It is evident from Figure 4 that the quaternary ammonium compounds have a structure which is similar in part to that of acetylcholine. It may also be noted that many of the anticholinesterase agents have a portion of their structure which resembles acetylcholine. By virtue of these similarities in structure, these compounds can replace acetylcholine in the tissues. However, although the compound replaces acetylcholine, it does not necessarily mimic it in its action. Any compound which has a structure similar to that of acetylcholine may have similar actions, as listed in Figure 4, that is, stimulation of cholinergic effector cells, stimulation of ganglion cells, stimulation of striate muscle, or combination with cholinesterase, and, in addition, may interfere with transmission at any of these sites. Quarternary ammonium compounds acting by each of these mechanisms have been described, and examples are shown in this diagram, as prepared by Leopold.[131] These compounds probably all demonstrate what is known as substrate competition, also illustrated in Figure 5.[131] These various compounds are competing for a place on an end-organ, an enzyme, or a ganglion cell. Compounds by virtue of their structure will vary in their velocity of reaction, their duration of effect, and their actual effect. Thus, it becomes apparent that new compounds may be formed that will replace acetylcholine more rapidly, and that other compounds may persist longer at this junction. It is also evident that a compound

TABLE 3.—*Variations in Effect of Anticholinesterase Agents*

	Neostigmine	Physostigmine	Diisopropyl Fluorophosphate (D. F. P.)
Ability to unite with cholinesterase	Short—reversible union	Longer—reversible union	Longest—irreversible union
Myasthenia gravis	Most pronounced improvement; short duration	Small improvement; short duration	Small improvement; long duration
Effects on central nervous system	Depression	Excitation	Excitation
Lipid solubility	Insoluble	Soluble	Soluble
Combined effect on pupil	Blocks D. F. P.; not blocked by D. F. P.	Blocks D. F. P.; not blocked by D. F. P.	Blocked by physostigmine and neostigmine; does not block neostigmine or physostigmine
Influence of pilocarpine on pupil	Reduces effectivness of neostigmine	Reduces effectiveness of physostigmine	Reduces effectiveness of D. F. P.

which has a structure similar to that of acetylcholine might act not only at one point but at several points in this neurohumeral scheme. It thus becomes apparent that agents called ganglion-blocking agents may have other varieties of function; for example, they may interfere with the transmission at the motor end-plate, as well as with the transmission at the ganglion. They might even have anticholinesterase properties. It is necessary to keep in mind that drugs that are labeled as ganglion-blocking agents are not necessarily that alone. Likewise, so-called cholinergic-blocking agents may have other properties.[131] Drugs which are labeled as anticholinesterase are not necessarily similar in all their other actions. Differences can be shown with each of the commonly used anticholinesterase agents (Table 3).[132]

Swan and Gehrsitz [133] present data indicating that when miotics are combined with the hope of obtaining more intense miosis and hypertensive effects than can be achieved by the use of a single drug, occasionally, instead of a synergistic or an additive action being obtained, a weaker miotic may reduce the effectiveness of a stronger drug.

131. Leopold, I. H.: Autonomic Drugs in Ophthalmology, read before the Chicago Ophthalmologic Society, Feb. 22, 1952.

132. Leopold, I. H.: Autonomic Drugs, read before the Pan-American Congress of Ophthalmology, Mexico, D. F., January, 1952.

133. Swan, K., and Gehrsitz, L.: Competitive Action of Myotics on the Iris Sphincter, A. M. A. Arch. Ophth. **46**:477, 1951.

Pilocarpine was found to decrease the reactivity of the iris sphincter of the albino rabbit to physostigmine and diisopropyl fluorophosphate, as well as to physiologically produced acetylcholine. The exact mechanism of this modifying action of pilocarpine remains to be established. The authors suggest that pilocarpine competes with acetylcholine for the receptor mechanism of the iris sphincter. If these conclusions are substantiated by further study, another possibility may be suggested.[132] The combination of these drugs may be one which allows an excess amount of acetylcholine to exist at the motor end-plate. It is known that acetylcholine in excess amounts causes depression of muscle, perhaps by spilling over onto the muscle fibers, causing depolarization of the muscle fiber itself. Depolarization of the muscle fiber blocks transmission of impulses, whereas depolarization of the end-plate causes an excitation wave to be transmitted to the muscle (Fig. 6). Therefore, in the presence of an excess amount of acetylcholine, such as might occur when one combines pilocarpine with an anticholinesterase agent in large quantity, depolarization of the muscle fiber may occur, leading to blockage of transmission, and thus may reduce the effect of the combination of agents. It must be realized, however, that in order that

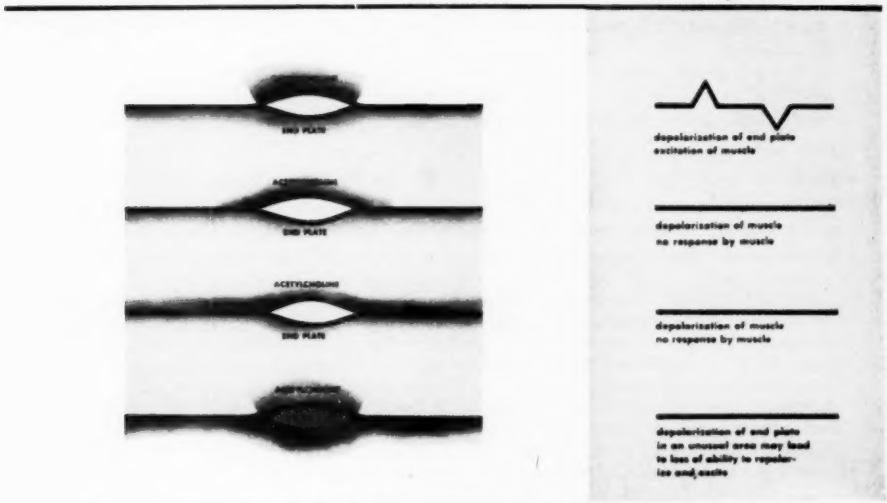
electrical response of muscle
depolarization of end plate
excitation of muscle
depolarization of muscle
no response by muscle
depolarization of muscle
no response by muscle
depolarization of end plate
in an unusual area may lead
to loss of ability to repolar-
ize and excite

Fig. 6.—Depolarization of end-plate and muscle to explain various actions of acetylcholine. Prepared by P. R. McDonald (Medical Treatment of Glaucoma, read before the New York Academy of Medicine, Section of Ophthalmology, Feb. 16, 1952) and Leopold, after the diagram of Feldberg (*Brit. M. Bull.* **6**:312, 1950.

such a depolarization of muscle fibers may be produced experimentally, large quantities of acetylcholine are required. This concept is simply a theory, and it remains to be seen whether the combination of pilocarpine and physostigmine, or of pilocarpine and diisopropyl fluorophosphate, allows such an excess of acetylcholine to accumulate.[132]

Numerous investigators have studied the action of various ganglion-blocking and cholinergic-blocking agents. It has been shown that the most active curariform agents contain nitrogen atoms and that these occur most commonly as fully ionized quaternary compounds, but are found also as active tertiary atoms. Diquaternary compounds are more active than monoquaternary compounds.

It is realized that there is a similarity between decamethonium iodide and tubocurarine chloride U. S. P. Neither of these compounds blocks conduction in motor nerves. Both block the effect of close arterial injection of acetylcholine without preventing the liberation of acetylcholine by motor-nerve stimulation. These are characteristics of so-called curariform action, but decamethonium iodide differs from tubocurarine chloride U. S. P. in that it is not antag-

onized by anticholinesterases. Also, a muscle partially blocked by decamethonium iodide responds to direct stimulation with a well-sustained contraction, while in a partially curarized preparation response falls off rapidly. Moreover, the fact that anticholinesterases do not antagonize decamethonium suggests that decamethonium and acetylcholine are not entering into the same type of competition as curare and acetylcholine. The problem is further complicated by the fact that under certain circumstances decamethonium and tubocurarine chloride can antagonize each other and that pentamethonium iodide can antagonize decamethonium iodide in concentrations which, by themselves, have no blocking action. Moreover, the potassium ion, which has an important antagonistic action on curare, does not antagonize decamethonium.[134] It is suggested by Paton and Zaimis [134c] that tubocurarine chloride acts by preventing acetylcholine from depolarizing the muscle membrane at the region of the end-plate and that the term "curariform" should be restricted to those drugs which act simply by raising the threshold of the motor end-plate to acetylcholine. They also state that the fundamental action of decamethonium is to depolarize the muscle-fiber membrane at the end-plate. This depolarization spreads beyond the region of the end-plate. This depolarization spreads beyond the region of the end-plate and forms a ring-like area of inexcitable membrane, about 2 mm. long, about the fiber (Fig. 6). The result of this is a neuromuscular block.[134n] Thus, decamethonium resembles in its action the huge doses of acetylcholine.

Curare has been tried in tetanus and found unsatisfactory because of the great risk of respiratory depression, and it has been used to block axonal conduction.[135]

Cholinergic-Blocking Agents.—A number of the cholingeric-blocking agents have been employed therapeutically. Prantal methylsulfate® [136] is thought to act primarily on the portion of the parasympathetic nervous system associated with gastric secretion and gastrointestinal motility. It produces no mydriasis in animals, and rarely in man, in doses which elicit this selective blocking action. A number of compounds are being investigated primarily for their ability to produce cyclo-

134. (*a*) Burns, B. D., and Paton, W. D. M.: Depolarization of the Motor End-Plate by Decamethonium and Acetylcholine, J. Physiol. **115**:41, 1951. (*b*) Taylor, D. B.: Some Basic Aspects of the Pharmacology of Synthetic Curariform Drugs, Pharmacol. Rev. **3**:412, 1951. (*c*) Paton, W. D. M., and Zaimis, E. J.: Actions and Clinical Assessment of Drugs Which Produce Neuromuscular Block, Lancet **1**:568, 1950. (*d*) Salama, A., and Wright, S.: Action in the Central Nervous System of Compounds RP3565 and RP3697 and of Tetramethyl Ammonium and Tetraethyl Ammonium, Brit. J. Pharmacol. **7: 1**: 1952; (*e*) Influence of Various Drugs on the Action of Curare on the Central System of the Cat, ibid. **7**:14, 1952. (*f*) Hey, P.: On Relationships Between Structure and Nicotine-Like Stimulant Activity in Choline Esters and Ethers, ibid. **7**:117, 1952. (*g*) Kunkel, A. M.; Oikemus, A. H., and Wills, J. H.: Bis-Quarternary Aliphatic Compounds, Federation Proc. **11**:365, 1952. (*h*) Harvey, S. C.; Bankal, J. L.; Blaser, G.; Heaton, F. W., and Stewart, L. H.: Interrelation of Autonomic Ganglionic Effects of Hexamethylene-Bis-Hemethylammonium and Tetraethylammonium, ibid. **11**:355, 1952. (*i*) Li, T. H.; Jacobs, B. R.; Aviado, D. M., Jr., and Schmidt, C. F.: Early Respiratory Depression by Curare and Curare-Potassium Antagonism, J. Pharmacol. & Exper. Therap. **104**:149, 1952. (*j*) Methonium Compounds in Hypertension, Letters to the Editor, Lancet **1**:642, 1951. (*k*) Hexamethonium Bitartrate, Letters to the Editor, ibid. **1**:797, 1951. (*l*) Douthwaite, A. H., and Thorne, M. G.: Effects of Hexamethonium Bromide on the Stomach, Brit. M. J. **1**:111, 1951. (*m*) Enderby, G. E. H., and Pelmore, J. F.: Controlled Hypotension and Postural Ischaemia to Reduce Bleeding in Surgery, Lancet **1**:663, 1951. (*n*) Bromism on Law-Salt Diets, Letters to the Editor, ibid. **1**:347, 1951. (*o*) Paton, W. D. M., and Perry, W. L. M.: Pharmacology of Toxiferines, Brit. J. Pharmacol. **6**:299, 1951.

135. Greenafest, H.; Nachmansohn, D.; Kao, C. Y., and Chambers, R.: Mode of Blocking of Axonal Activity by Curare and Inhibitors of Acetyl Cholinesterase, Nature, London **169**:190, 1952.

136. Margolin, S.; Doyle, M.; Giblin, J.; Makovsky, A.; Sprerlein, M. T.; Stephens, I.; Berchtold, H.; Belloff, G., and Tislow, R.: Pharmacological Properties of a New Parasympathetic Blocking Agent, N,N-Dimethyl 4-Piperidylidene 1,1 Diphenylmethane Methyl Sulfate (Prantal), Proc. Soc. Exper. Biol. & Med. **78**:576, 1951

plegia and mydriasis [137] and to act as adequate substitutes for atropine and homatropine.[137]

Scopolamine has been shown to produce disorientation and ataxia. This occurs more frequently in elderly people with arteriosclerosis, in whom urinary excretion of the drug is delayed by the reduced renal function.[138] Methantheline (banthine®) has been reported to have some merit in treatment of herpes zoster.[139] Studies of the influence of atropine on the sympathetic ganglia have led to discrepant results, and probably most of these can be explained by a difference in experimental conditions and methods.[140] Reiter [141] calls attention to the potent effects of a combination of phenylephrine (neo-synephrine®) hydrochloride and eucatropine hydrochloride in 1% methylcellulose solution. This solution is stable for two months; it produces a rapid and potent mydriatic effect, and the duration of effect is four to six hours. Rycroft and Romanes [142] point out that a bloodless field of operation can be produced by the use of hexamethonium with a suitable posture in the case of operations in and round the orbit, where bleeding would impair efficient accurate surgery. This procedure may have merit in a case of severe acute glaucoma requiring surgical treatment with the patient under general anesthesia. Loss of blood is eliminated; postoperative edema due to manipulation is reduced, and secondary fibrosis of coarse, unorganized clots may be avoided. However, the method requires the attention of a skilled anesthestist until normal blood pressure has been established on the patient's return to bed. Epinephrine is contraindicated.[142]

Other Agents.—The response of ocular movements to amobarital and mephenesin has been studied by Berger and associates [143] and by Bender and associates.[144] In subjects with preexisting nystagmus, acquired or congenital, amobarbital caused disappearance of nystagmus. Response to mephenesin was similar. However, higher doses were required of the latter drug, and the effects were not as constant. Both these agents produced nystagmus on lateral, upward, and downward gaze and have the power of abolishing optokinetic nystagmus.

Amine Oxidase.—The nictitating membrane of the cat and the pupil have been shown to be less sensitive to arterenol than to epinephrine. After denervation the two drugs are about equally effective. It has been suggested that arterenol is more rapidly destroyed than epinephrine, and this could account for the difference in reaction, for, as Burn and Robinson [145] recently showed, amine oxidase has a greater affinity for arterenol than for epinephrine. Amine oxidase has been found in the iris and nictitating membrane of the cat and has been

137. Kiess, R. D., and Fralick, F. B.: A Preliminary Report on a New Cycloplegic and Mydriatic Drug, Am. J. Ophth. **34**:1593, 1952. Priestley, B. S., and Medine, M. M.: New Mydriatic and Cycloplegic Drug, ibid. **34**:572, 1951. Feldman, J. B.: Lachesine (E_8), ibid. **34**:442, 1951. Drucker, A. P., and Kazort, R. J.: Clinical Trial of a New Atropine-Like Drug, ibid. **34**:847, 1951. Gettes, B., and Leopold, I. H.: Cholinergic Blocking Agents in Ophthalmology, read before the Fourth Wills Hospital Clinical Conference, March 22, 1952.

138. Herzog, H.: Additional Comment Regarding Toxic Manifestations After the Application of Scopolamine Ointment to the Eye, Klin. monatsbl. Augenh. **118**:636, 1951.

139. Brown, H. S.; Reekie, R. D., and Sinclair, W. J.: Acute Herpes Zoster Treated with Banthine, Northwest Med. **50**:432, 1951.

140. Tuede, K. M., and Cahea, R. L.: Action of Atropine on Sympathetic Ganglia, Federation Proc. **11**:398, 1952.

141. Reiter, C.: A New Synergistic Mydriatic Combination, Am. J. Ophth. **35**:412, 1952.

142. Rycroft, B. W., and Romanes, G. J.: Preliminary Report on the Use of Methonium Compounds and General Anesthesia in Ophthalmic Surgery, Brit. J. Ophth. **36**:29, 1952.

143. Berger, P. S.; Nathanson, M., and Bender, M. B.: Electrical Recordings of Normal and Abnormal Eye Movements Modified by Drugs, A. M. A. Arch. Neurol. & Psychiat. **67**:357, 1952.

144. Bender, M. B.; Nathanson, M., and Green, M.: Effect of Intravenous Tolserol in Normal and Abnormal Ocular Movements, Am. J. Ophth. **34**:579, 1951.

145 Burn, J. H., and Robinson, J.: Noradrenalin and Adrenaline in Vessels of the Rabbit Ear in Relation to Action of Amine Oxidase, Brit. J. Pharmacol. **6**:101, 1951.

demonstrated in the large and small arteries and veins of the rabbit.[146] Thompson and Tickner[147] indicate that amphetamine is a more potent inhibitor of amine oxidase than is ephedrine and that methylene blue and dibucaine (nupercaine®) are also potent in this respect. In 1908, Eppinger, Falla, and Rudinger found in dogs from which the thyroid was removed that the injection of epinephrine did not cause glycosuria. It is known that amine oxidase is present in the liver and that this enzyme can destroy epinephrine. The effect of a given amount of epinephrine in producing hyperglycemia may, therefore, depend on the amount of amine oxidase present. Thyroid feeding causes the amine-oxidase activity of the liver of rabbits to decrease; thyroidectomy causes it to rise.[148]

Vessel Caliber.—Using angioscotometry as a method of measuring the caliber of the retinal vessels, Fink[149] has demonstrated inhibition by thiamine hydrochloride of the retinal responses produced by nicotine. The subcutaneous injection of 100 mg. of thiamine hydrochloride prior to the smoking of one cigaret with inhalation contributed to the inhibition of the angioscotomal alterations. This was not found when the cigaret was smoked without previous injection of thiamine.

It has been shown that the caliber of the retinal vessels can be reduced by immersion of the hands in cold water—that is, the cold pressor test of Hinds and Brown. When the hands are dipped in hot water, in some subjects the vessels dilate; in others no change occurs, and in others the vessels dilate after a considerable period.[150] Yamagishi[151] found that the pressure in the retinal arteries was between 56 and 67% of the pressure in the brachial artery, and that with warm compresses on the eye for 15 minutes at 45 C. the pressure in the retinal arteries decreased. With infrared irradiation no significant change occurred in the pressure of the retinal arteries for 10 minutes, but within 30 minutes it was definitely increased, and with ultra-short-wave irradiations to the eye the arterial pressure in the retina definitely increased.

Amyl nitrite caused dilatation of the retinal blood vessels, the arteries being affected more than the veins. Subcutaneous injection of 1% sodium nitrite, 1 to 6 ml., produced dilatation of the retinal vessels. In 75% of the subjects given 0.1 to 0.2 gm. of sodium nitrite by mouth, dilatation also occurred.[152]

It has been possible to show that retrobulbar injection of 0.25 ml. of a solution of 1:1,000 epinephrine hydrochloride can produce a decrease in the size of the angioscotomas in young normal subjects.[153] Zahn[154] has demonstrated that nicotinic acid, given in a dose of 0.2 gm. may produce changes in the caliber of the retinal vessels, as determined by angioscotometry.

Favorable results with the oral administration of benzazoline (priscol®) as a vasodilator were noted in three cases of angiospastic processes in the retina, one case of optic neuritis, and one case of neuroparalytic keratitis. Benzazoline, which has a direct histamine-like action

146. Robinson, J.: Amine Oxidase in the Iris and Nictitating Membrane of the Cat and the Rabbit, Brit. J. Pharmacol. **7**:99, 1952. Thompson, R. H. S., and Tickner, A.: Amine Oxidase in the Large and Small Arteries and Veins of the Rabbit, J. Physiol. **115**:34, 1951. Burn and Robinson.[145]

147. Thompson, R. H. S., and Tickner, A.: The Occurrence and Distribution of Monoamine-Oxidase in Blood Vessels, J. Physiol. **115**:34, 1951.

148. Spink, A., and Burn, J. H.: Thyroid Activity and Amine Oxidase in the Liver, Brit. J. Pharmacol. **7**:93, 1952.

149. Fink, A. I.: The Inhibition of Thiamine Chloride on the Retinal Responses Caused by Nicotine, Am. J. Ophth. **34**:139, 1951.

150. Iitsuka, T.: The Study of Micrometry of the Retinal Vessels, Acta Soc. Ophth. Jap. **55**:170, 1951. Henkes, H. E.: The Use of Electroretinography in Measuring the Effect of Vasodilatation, Angiology **2**:125, 1951. Bonamour, G.: The Choice and Method of Use of Vasodilators in Retinal Vascular Occlusions, Ann. ocul. **184**:729, 1951.

151. Yamagishi, H.: The Effect of Physical Influences on the Retinal Arterial Blood Pressure, Acta Soc. ophth. jap. **55**:197, 1951.

152. Iwanaga, T.: Effects of the Nitrite Group on the Caliber of the Retinal Vessels, Acta Soc. ophth. jap. **55**:178, 1951.

153. Ferrata, L.: Action of Vasoconstrictors and Angioscotometry, Ann. ottal. e clin. ocul. **77**:115, 1951.

154. Zahn, K.: Influence of Nicotinic Acid on Angioscotomata, Československ. ofth. **7**:407, 1951.

on blood vessels in small doses and produces adrenergic block in large doses, when used intravenously in doses of 50 mg., produced dilatation of retinal vessels, as determined by angioscotometry. The maximum effect took place 15 to 20 minutes after injection. In eyes in which there was visible evidence of extensive vessel-wall fibrosis, no dilatation could be noted.[155] One case of glaucoma following parenteral use of benzazoline is reported.[155g] Frede[156] found an ointment containing 10% benzazoline to be helpful in cases of lime burns of the conjunctiva. He finds this drug desirable to use in chronic intraocular disease in which active hyperemia is desirable. The drug may be injected into the anterior chamber in 0.5 to 1% solution or into the vitreous body, in which case 1 to 10 drops of a 1 to 10% solution are injected through the region of the ora serrata. He describes beneficial effects in retinitis pigmentosa. Loss of peripheral vascular reactivity occurs in potassium deficiency.[157]

Coston[158] and others[159] recommend that stellate-ganglion block with procaine be done early in all cases of sudden visual failure thought to be due to vascular occlusion either in the eye or of cerebral origin.

Responsiveness to vasoactive drugs in dogs has been found to be sharply reduced after suppression of thyroid function with radioactive iodine or propylthiouracil or by surgical thyroidectomy. Tetraethylammonium chloride, however, was an exception.[160] Papaverine, one of the benzyl isoquinoline derivatives of opium, has found its primary usefulness in relaxation of the smooth muscle of blood vessels.[161] Shenken[162a] failed to note any effect of the various drugs tried on the cerebral circulation except for some reduction in cerebrovascular resistance, which may have been due to relaxation of the smooth muscle coats of the arteries and arterioles. Leopold was unable to demonstrate any change in the caliber of the larger choroidal vessels with any of the vasodilator or vasoconstrictor agents tried.[110]

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155. (*a*) Stern, J. J.: Priscoline, a New Vasodilator, Am. J. Ophth. **35**:187, 1952. (*b*) Cholst, M. R.; Schilback, H. F.; Handelsman, M. B., and Levitt, L. M.: Retinal Response to Priscoline, Am. J. Ophth. **35**:191, 1952; (*c*) Response of the Retinal Vessels to Priscoline in Diabetes Mellitus, ibid. **35**:375, 1952. (*d*) Frank, N.; Strazza, J. A., Jr., and Helsber, J. T.: Effects of Priscol in Treatment of Peripheral Vascular Diseases, Ann. Int. Med. **35**:19, 1951. (*e*) Selecka, I.: Priscol in Therapy of Degenerative Myopia, Československ. ofth. **7**:209, 1951. (*f*) Zarrabi, M.: Observations on Priscol in Ophthalmology, Ophthalmologica **122**:76, 1951. (*g*) Gallois, J.: Acute Glaucoma Following Priscol Administration, Bull. Soc. ophth. France **2**:131, 1951.

156. Frede, R.: Use of Priscol in Chronic Eye Disease with Particular Reference to Intravitreous Injection, Med. Klin. **46**:519, 1951.

157. Rosenman, R. H.; Freed, S. C., and Friedman, M.: The Peripheral Vascular Reactivity of Potassium Deficient Rats, Circulation **5**:412, 1952. Friedman, M.; Freed, S. C., and Rosenman, R. H.: Effect of Potassium Administration on (1) Peripheral Vascular Reactivity and (2) Blood Pressure of the Potassium Deficient Rat, ibid. **5**:415, 1952.

158. Coston, T. O.: Ocular Symptoms of Stellate Ganglion Block, Am. J. Ophth. **34**:1289, 1951.

159. (*a*) Scott, D. H.: Stellate Ganglion Block for Cerebrovascular Accident Involving Homonymous Hemianopsia, A. M. A. Arch. Ophth. **45**:471, 1951. (*b*) Leriche, R.: Treatment of Embolism and Thrombosis of the Cerebral Vessels, Brit. M. J. **1**:231, 1952. (*c*) Vascular Spasm, editorial, ibid. **1**:93, 1952.

160. Page, I. H., and McCubbin, J. W.: Influence of Thyroidal Function on Vascular Reactivity in Dogs, Circulation **5**:390, 1952. Page, I. H.: Humoral and Vasomotor Controls of Blood Vessels, Bull. New York Acad. Med. **28**:131, 1952.

161. Sayne, H. W.; Scheinberg, P.; Rich, M., and Belle, M. S.: Effect of Intravenous Papaverine Hydrochloride on the Cerebral Circulation, J. Clin. Invest. **31**:111, 1952.

162. (*a*) Shenkin, H. A.: Effect of Various Drugs Upon Cerebral Circulation and Metabolism of Man, J. Appl. Physiol. **3**:465, 1951. (*b*) Morita, S.: Experimental Studies of the Relation Between the Pituitary Body and Intraocular Pressure, Acta Soc. Ophth. Jap. **55**:134, 1951. (*c*) Goodwin, R. C.: Changes in the Intraocular Pressure in Normal and Glaucomatous Eyes Following Furmethide, Am. J. Ophth. **34**:1139, 1951.

Drugs Affecting Intraocular Pressure.—After the subcutaneous injection of anterior pituitary extract, called "praehormone," a fall in intraocular pressure occurred slowly, with a return to its former level within 24 hours. Subsequent injections seemed to have no influence.[162b] Changes in blood pressure paralleled those in intraocular pressure. Subcutaneous injections of posterior pituitary, called "contramin," produced a fall in intraocular pressure after one hour, and after three hours it rose to a level higher than the original. The blood pressure did not parallel the intraocular pressure after these injections. After partial hypophysectomy the intraocular pressure rose slightly. Total hypophysectomy failed to influence the intraocular pressure.

Goodwin [162c] was interested in whether there was any characteristic difference in the fall of intraocular pressure following the use of furtrethonium (furmethide®) in normal eyes and in eyes with primary wide-angle or narrow-angle glaucoma, in each of which the initial pressure was 30 mm. Hg or less. Goodwin's experience suggests that the response of intraocular pressure to furtrethomium iodide in 10% solution cannot be used as a therapeutic test in the diagnosis of glaucoma. Eyes with narrow-angle glaucoma in an acute congestive attack appeared to respond very slowly to furtrethomium as compared with eyes with elevated tension but without congestive signs.

A high order of muscarine activity has been found in furtrethonium iodide. This, however, can be excelled 10-fold by its 5-methyl analogue (5-methylfurfuryltrimethylammonium iodide [methyl fumethide®]). This agent is 10 times as potent as furthrethomium when injected intraperitoneally and two times as potent as carbachol; and it also appears not to be too toxic for clinical use. These studies suggest that methyl furthrethomium is worthy of clinical application, particularly in glaucoma.[163]

"Ts-219," a Czechoslovakian preparation, is identical with "mintacol" (diethyloxyphosphor acid-p-nitrophenyl ester). TS-219 [164] is used in a concentration of 1:6,000 in aqueous solution. It is effective in all forms of glaucoma, but the dose must be adapted to each patient. Its effect exceeds that of pilocarpine or physostigmine, but does not equal that of diisopropyl fluorophosphate.[164].

Hormones have been shown to have variable effects in intraocular pressure. Testosterone is claimed to raise the intraocular pressure,[165] and the hormone of the corpus luteum has been reported to have no effect, in contradistinction to an early report of Obal's mentioned in last year's review, which showed this hormone to have a synergistic effect with miotics.[166]

Davson and Matchett [167] have shown that the intraocular pressure in the rabbit eye can be increased by the subconjunctival injection of nitrogen mustard or by section of the postganglionic fibers of the cervical sympathetic nerve. Stimulation of the peripheral end of the cut nerve always caused a fall in intraocular pressure. These authors conclude that changes in intraocular pressure following both sympathectomy and injection of nitrogen mustard are mediated by purely vascular mechanisms.

Comparisons of the effects of pilocarpine, carbachol, and physostigmine on intraocular pressure showed that physostigmine was the most efficient, although it had the most undesirable side-effects, such as severe headache.[168]

Many instances are known to ophthalmologists in which an attack of acute glaucoma has been preceded by emotional shock. The connection between the autonomic nervous system and glaucoma has been reviewed with regard to the psychogenesis of this disorder.[169] Experiments

163. Lourie, E. M.: Pharmacological Effects of Some Derivatives of Furan and Choline, Brit. J. Pharmacol. **7**:130, 1952. Grewal, R. S.: Methyl Furmethide, ibid. **6**:696, 1951.

164. Iselle, R.: Synthetic Miotic TS219, Československ. ofth. **7**:174, 1951.

165. Radnot, M.: Effect of Hormones in Cases of Glaucoma, Szemészet ophth. Hungary **88**:114, 1951.

166. Treumer, K.: Treatment of Glaucoma with Lutein Hormone, Klin. Monatsbl. Augenh. **118**:644, 1951.

167. Davson, H., and Matchett, P. A.: The Control of the Intraocular Pressure in the Rabbit, J. Physiol. **113**:387, 1951.

168. Eidelman, V. M.: The Comparative Action of Carbachol, Pilocarpine, E. serin and Proserine on the Intraocular Tension, Vestnik. oftal. **30**:34, 1951.

169. van Alphen, G. W. H. M., and Stokvis, B.: Psychosomatic Aspects of Intraocular Pressure, Nederl. tijdschr. geneesk. **95**:2246, 1951.

revealed, however, that very severe emotional shock exerts no influence on the ocular pressure in persons with normal eyes. With the aid of a hypnotic method, it was possible to establish correlations between ocular pressure and emotional conditions in cases of psychogenic glaucoma.

Miscellaneous Drugs.—Keasling and associates[170] found that subconjunctival injection of physostigmine produces significant corneal anesthesia in the rabbit. The degree of anesthesia was not affected by the additional use of procaine, either locally or subconjunctivally. They found the same results to follow the use of pilocarpine or carbachol. This entire phenomenon could be blocked by the prior instillation of atropine. This evidence is somewhat opposed to that presented by Grieg, Holland, and Lindvig,[171] in last year's review. In their article they expressed the belief that the prior use of an anticholinesterase agent allowed better anesthesia to be obtained by such poorly penetrating drugs as procaine.

Apter[172] has shown once again that dilation of the pupil by cocaine may cause a pupil to react promptly to light which prior to use of cocaine apparently failed to react to the usual light stimulus.

Intravenous Injection of Alcohol.—When administered parenterally, alcohol has been found to exert sedative, hypnotic, analgesic, euphoric, vasodilator, caloric, and antipyretic effects. Alcohol belongs to the group of cerebral depressants and lessens the sensitivity to pain.[173] It affects first the cerebrum, then the spinal cord, and, last of all, the respiratory centers, while morphine depresses the respiratory centers and the cerebrum simultaneously and, to a less extent, the reflex excitability of the cord. Therefore, alcohol should prove more effective as a postoperative sedative than morphine. Therapeutic doses of alcohol administered intravenously usually result in mental sedation, with dulling of memory, insight, and power of concentration. Thinking is fairly normal, and there is no "doped" feeling; rather, the subject has a sense of well-being and loss of anxiety. Nausea and vomiting do not occur. It is best to judge the rate of infusion by the subjective signs. Since the normal person metabolizes approximately 10 cc. of pure alcohol per hour, it will require 200 cc. of 5% alcohol solution to obtain 10 cc. of 95% alcohol. In the average patient this amount is entirely metabolized in one hour. The alcohol in excess of 10 cc. per hour accumulates in the blood stream and is responsible for the desired analgesia, euphoria, and loss of anxiety, and for the best clinical results. Therefore, it is best to judge the rate of infusion by subjective signs. No reports of this treatment in ophthalmology could be found. It does not seem fair to deprive ophthalmic patients of this delightful therapy.

ANTICOAGULANTS

Influence of Drugs on Blood Coagulation.[174]—Bishydroxycoumarin U. S. P. (dicumarol®) decreases the prothrombin concentration of plasma. Its action is on the liver, and it may be that the drug itself, rather than one of its derivatives, produces this effect. Bishydroxycoumarin

170. Keasling, H. H.; Featherstone, R. M.; Schueler, F. W., and Gross, E. G.: Further Observations on Anesthetization of Rabbit's Cornea by Non-Surface Anesthetics, Proc Soc. Exper. Biol. & Med. **77**:31, 1951.

171. Grieg, M. B.; Holland, W. C., and Lindvig, P. E.: Anesthetization of the Rabbit's Cornea by Nonsurface Anesthetics, Brit. J. Pharmacol. **5**:461, 1950.

172. Apter, J. G.: Significance of the Unilateral Argyll Robinson Pupil, read before the Chicago Ophthalmological Society, Jan. 21, 1952.

173. Karp, M., and Sokol, J.: Intravenous Use of Alcohol in a Surgical Patient, J. A. M. A. **146**:21, 1951.

174. (*a*) Seegers, W. H.: Influence of Certain Drugs on Blood Coagulation and Related Phenomena, Pharmacol. Rev. **3**:278, 1951. (*b*) Wright, I. S.: Pathogenesis and Treatment of Thrombosis, Circulation **5**:161, 1952. (*c*) Rehbein, A.; Jaretski, A., and Habif, D. V.: Response of Dicoumarol-Induced Hypoprothrombinemia to Vitamin K, Ann. Surg. **135**:454, 1952. (*d*) Gruber, C. M.; Lee, K. S., and Rieders, F.: Absorption, Distribution and Activity of Tromexan, Federation Proc. **11**:352, 1952. (*e*) Stirling, M., and Hunter, R. B.: Pharmacology of Bis 3-3'-(4 Oxycoumarinyl) Ethyl Acetate (Tromexan), Lancet **2**:611, 1951. (*f*) Mangieri, C. N.; Engelberg, R., and Randall, L. O.: The Heparin-Like Activity of a New Anticoagulant, Treburon, J. Pharmacol. & Exper. Therap. **102**:156, 1951. (*g*) Lituras, J.; Vorzuner, J. J.;

(Footnote continued on next page)

produces a transitory decrease in plasma AC-globulin and probably affects the plasma concentration of one or more of the new blood-coagulation factors which have been discovered recently.[174]

Vitamin K accelerates recovery from bishydroxycoumarin-prothrombin depression.

When intravenously administered, purified prothrombin restores the prothrombin concentration of the blood to the normal level.

Several compounds related to bishydroxycoumarin produce essentially the same qualitative effects as those produced by bishydroxycoumarin itself. Qualitative differences are found, however, such as the rapidity with which prothrombin concentration falls when the compound is administered and the rapidity with which it rises when the compound is withdrawn.

Salicylates in large quantities produce hypoprothrombinemia. One can prevent or reverse this with vitamin K.

Methylxanthine in large doses makes the blood hypercoagulable. One of the contributing factors is an increase in plasma AC-globulin concentration.

Antibiotics are reported to produce hypercoagulable blood. The evidence is not definite, however. Protamine given intravenously neutralizes the effect of injected heparin. Protamine disappears from the blood within a few hours.

Toluidine blue has an antiheparin effect, which develops slowly and is still detectable 24 hours after initial injection.

Cardiac glycosides produce hypercoagulable blood due to increase of the AC-globulin concentration.

Sussman, L. N.; Applezweig, M., and Etiss, A. D.: Sublingual Administration of Heparin, Proc. Soc. Exper. Biol. & Med. **77**:325, 1951. (*h*) Manchester, B.; Sageman, C. B.; Rabkin, B., and Hill, E. B.: Experience with the New Anticoagulant Paritol C, Ann. West. Med. & Surg. **6**:209, 1952. (*i*) Hour, G. W.; Armbrust, C. A., Jr.; Levy, M. D., and Wagner, E. L.: Preliminary Report of the Antirheumatic Action of Heparin and Paritol C, Am. J. M. Sc. **223**:258, 1952. (*j*) Glick, D., and Sylvén, B.: Evidence for the Heparin Nature of the Nonspecific Hyaluronidase Inhibitor in Tissue Extracts and Blood Serum, Science **113**:388, 1951. (*k*) Crane, C.: Use of Heparin-Gelatin-Dextrose in Venous Thrombosis and Pulmonary Embolism, New England J. Med. **245**:926, 1951. (*l*) Cartasegna, F.: Treatment of Thrombosis of the Retinal Veins with Dicoumarol, Rass. ital. ottal. **20**:153, 1951. (*m*) Gasparri, F.: Anticoagulant Treatment in Venous Thrombosis of the Retina, Boll. ocul. **30**:309, 1951. (*n*) Wellman, E. W., and Allen, E. B.: Variable Effects of Identical Amounts of Dicoumarol on Prothrombin Values of Different Persons, Proc. Staff Meet., Mayo Clin. **26**:257, 1951. (*o*) Tullock, J. A., and Gilchrist, A. R.: Tromexan in the Treatment of Coronary Thrombosis, Am. Heart J. **42**:864, 1951. (*p*) Antibiotics and Blood Coagulation, editorial, New England J. Med. **246**:240, 1952. (*q*) Long, C. N.: Antibiotics and Blood Coagulation, J. A. M. A. **142**:49, 1950. (*r*) Macht, D. I.: Influence of Some Drugs and of Emotions on Blood Coagulation, ibid. **148**:265, 1952. (*s*) Duff, I. F.; Falls, H. F., and Linman, J. W.: Anticoagulant Therapy in Occlusive Vascular Disease of the Retina, A. M. A. Arch. Ophth. **46**:601, 1951. (*t*) Zwiauer, A., and Deutsch, E.: Influence of the Prothrombin Level on the Coagulation of Albumin in the Aqueous of the Anterior Chamber, von Graefes Arch. Ophth. **151**:744, 1951. (*u*) Elrod, P. D.; McCleery, R. S., and Ball, C. O. T.: An Experimental Study of the Effect of Heparin on Survival Time Following Lethal Burns, Surg. Gynec. & Obst. **92**:35, 1951. (*v*) Zwiauer, A.; Bornschein, H., and Deutsch, E.: Effect of Anticoagulants on the Clotting in the Plasmoid Fluid and Its Significance for the Intraocular Pressure, Am. J. Ophth. **34**:1403, 1951. (*w*) Hanson, H.; Mann, F., and Barker, N. W.: Clinical Experience with Anticoagulant No. 63, Circulation **4**:844, 1951. (*x*) Coon, R. W.; Flynn, J. E., and Vassar, P. S.: In Vivo and in Vitro Effects of a Lipid Inhibitor of Blood Clotting, Federation Proc. **10**:352, 1951. (*y*) Barker, N. W.; Hanson, H. H., and Mann, F. D.: Bishydroxycoumarin, Ethyl Biscoumacetate and 4-Hydroxycoumarin Anticoagulant No. 63, J. A. M. A. **148**:274, 1952. (*z*) Overman, R. S.; Sorenson, C. W., and Wright, I. S.: Effectiveness of Synthetic Water-Soluble Vitamin K Preparations in Bishydroxycoumarin-Induced Hypoprothrombinemia, ibid. **145**:393, 1951. (*a'*) Watkin, D. M.; Van Italie, T. B.; Logan, W. B.; Geyer, R. P.; Davidson, C. J., and Stone, F. J.: Treatment of Dicoumarol-Induced Hypoprothrombinemia in Man with Emulsified Vitamin K, Administered Intravenously, J. Lab. & Clin. Med. **37**:269, 1951.

Alpha-tocopherol decreases the incidence of thrombosis by its action on antithrombin. The evidence for this, however, is slight.

Heparin produces an immediate anticoagulant effect. Its action is twofold. It blocks the activity of prothrombin, and it interferes with the action of thrombin on fibrinogen. The duration of action of heparin is limited to several hours. There are various repository forms which prolong the action. The chief difficulty with repository forms has been their toxicity.

Sulfonamides produce their effect by eliminating the intestinal bacteria which produce vitamin K, and thus reduce the coagulability.

In poor nutrition less vitamin K and other coagulating substances will be formed, so that the coagulating property of the blood is reduced.

Corticotropin and cortisone probably produce hypercoagulability of the blood, but the evidence is not absolute.

With the exception of chloroform, anesthetic agents produce no profound effects on the coagulability of the blood. Deep chloroform anesthesia decreases prothrombin, AC-globulin, and fibrinogen concentration of the blood. This is the result of induced hepatic damage.

Epinephrine produces hypercoagulability of the blood.

Acetylcholine has an opposite effect and can apparently alter the blood, so that fibrinolysis occurs in blood taken from the vein after acetylcholine-induced shock.

Blood-Coagulation Components Prepared in Concentrated Form.—Prothrombin may be applied directly to wounds. To date, there has been no untoward antigenic reaction from such local applications. Streptokinase and streptodornase have a fibrinolytic and a proteolytic action, and thromboplastin also is an aid in the clotting mechanism.[174a,b]

Therapy of Thrombosis.—A successful attack on thrombosis requires (*a*) prevention of its original development, (*b*) prevention of spread or multiplication of any already formed thrombus, (*c*) encouragement of the dissolution of the original thrombus, and (*d*) discouragement of spread of the existing thrombus. Failures occur with all anticoagulants. Uniform response cannot be obtained in all cases, and there is always the risk of hemorrhage.[175]

There are several new anticoagulants—tromexan® (ethyl bis-[4-hydroxy-2-keto-3-α-benzopyranyl] acetate),[174d-f] phenylindanedione, 4-hydroxycoumarin anticoagulant 63,[174w] paritol®,[174h] and a lipid thromboplastin inhibitor.[176] Tromexan® can be administered orally; it produces a rapid increase in the prothrombin time, the response reaching a maximum in 12 to 24 hours after a 90-mg. dose. The return to normal is almost as prompt.

Phenylindanedione is comparable in its speed of action to tromexan.® However, its action is less predictable, and it is not counteracted by vitamin K.

4-hydroxycoumarin anticoagulant 63 is two to three times as potent per unit weight as is bishydroxycoumarin and 10 to 15 times as potent per unit weight as tromexan.®

Paritol® is similar to heparin in both chemical structure and action. The duration of effect is longer than that of heparin. The adverse effects from its use are shock, vasomotor collapse, urticaria, and elevation of the blood urea nitrogen. The lipid thromboplastin inhibitor is an inositol phosphatide fraction of rabbit brain, of soybean, and of plasma phosphatides.

Vitamin K_1 (2-methyl-3-phytyl-1,4-naphthoquinone) emulsion can be administered intravenously and is effective in overcoming hypoprothrombinemia due to bishydroxy coumarin, tromexan,® phenylindanedione, and anticoagulant 63. A dose of 50 mg. is usually successful in six hours, irrespective of degree of hypoprothrombinemia. The dose may have to be repeated in 12 hours. When smaller doses of bishydroxycoumarin are used, smaller doses of vitamin K_1 will be satisfactory.[177]

Paritol-C® (polysulfuric acid ester of polyanhydromannuronic acid) has a definitely favorable antirheumatic action, as has heparin. One may not say whether this is due to an antihyaluronidase activity or to an anticoagulant or an antiexudative action.

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175. Wright.[174b] Rehbein, Jaretski, and Habif.[174c] Gruber, Lee, and Rieders.[174d] Stirling and Hunter.[174e] Mangieri, Engelberg, and Randall.[174f] Lituras and others.[174g] Manchester and others.[174h] Crane.[174k] Cartasegna.[174l] Gasparri.[174m] Tullock and Gilchrist.[174o] Duff, Falls, and Linman.[174s]

176. Wright.[174b] Coon, Flynn, and Vassar.[174x]

177. Watkin and others.[174a'] Rehbein and others [174c] Overman, Sorenson and Wright.[174s]

There is also the possibility of these agents being antianaphylactic, or they may influence antigen-antibody reactions.[174i-j]

One cannot emphasize too strongly that there is no constantly correct dose of bishydroxycoumarin, and that the treatment with this drug can be safe and efficient only when the prothrombin time is determined repeatedly at short intervals.[174n]

Duff and his co-workers [174s] conclude that the use of anticoagulant therapy favorably influences the prognosis for visual improvement after retinal vascular occlusion and reduces the incidence of secondary glaucoma. Short-term therapy with heparin produced results approximately the same as those following the prolonged use of bishydroxycoumarin. The incidence of the complication of hemorrhage, however, is much more pronounced in long-term treatment with bishydroxycoumarin. Thus, by using the short-term therapy, they obtained equally good results, without the same danger of hemorrhagic complications. These authors also recommend prompt therapy after thrombosis or occlusion of a retinal artery if results are to be favorable.[174s] Satisfactory results have been reported by others [174l-m] in thrombosis of retinal veins. Zwiauer, Bornschein, and Deutsch found that when prothrombin activity fell below 30% no coagulation could be obtained in the anterior chamber of the rabbit eye after paracentesis. With a prothrombin activity between 30 and 70% there was a noticeable reduction in the fibrin formation.[178] There is also evidence that heparin may be of value in the therapy of burns.[174u]

RADIATION

It is well known that some tissues of the body are more sensitive to radiation than others.[179] Cells that are dividing and reproducing rapidly are more affected

178. Zwiauer and Deutsch.[174t] Zwiauer, Bornschein, and Deutsch.[174v]

179. (*a*) Spoerl, E.: The Lethal Effects of Radiation, Scient. Am. **185**:*22* (Dec.) 1951. (*b*) Wolf, B. S.: Mechanism of Biological Effects of Radiation, J. Mt. Sinai Hosp. **18**:330, 1952. (*c*) Hempelman, L. H.; Lisco, H., and Hoffman, J. G.: The Acute Radiation Syndrome, Ann. Int. Med. **36**:279, 1952. (*d*) Christenberry, K. W., and Furth, J.: Induction of Cataracts in Mice by Slow Neutrons and X-Rays, Proc. Soc. Exper. Biol. & Med. **77**:559, 1951. (*e*) Cogan, D. G., and Donaldson, D. D.: Experimental Radiation Cataracts, A. M. A. Arch. Ophth. **45**:508, 1951. (*f*) Cogan, D. G.; Donaldson, D. D., and Reese, A. B.: Clinical and Pathological Characteristics of Radiation Cataract, ibid. **47**:53, 1952. (*g*) Kimura, S. J., and Ikui, H.: Atomic Bomb Radiation Cataract, Am. J. Ophth. **34**:811, 1951. (*h*) Rabinowitz, A.: Medical Aspects of the Atomic Bomb, South African M. J. **25**:488, 1951. (*i*) von Sallmann, L.; Munoz, C. M., and Barr, E.: Experimental Studies on Early Lens Changes After Roentgen Irradiation, A. M. A. Arch. Ophth. **47**:305, 1952. (*j*) von Sallmann, L.; Dische, Z.; Ehrlich, G., and Munoz, C. M.: Study on Penetration of Cysteine and Cystine into the Aqueous Humor of Rabbits and Its Relation to Early X-Irradiation Effects on the Eye, Am. J. Ophth. **34**:95, 1951. (*k*) von Sallmann, L., and Munoz, C. M.: Further Efforts to Influence X-Ray Cataract by Chemical Agents, A. M. A. Arch. Ophth. **47**:21, 1952. (*l*) Slepyan, A. H., and Cornbleet, T.: Cysteine as a Local Protective to Human Skin Against X-Rays, A. M. A. Arch. Dermat. & Syph. **64**:425, 1951. (*m*) Trovati, E.: Visual Disturbances and Temporary Ophthalmoscopic Changes in Children After Cranial Roentgen Therapy for Ringworm, Ann. ottal. e clin. ocul. **77**:127, 1951. (*n*) Brattgard, S. O.: The Study of the Effects of X-Ray on the Ganglionic Cells of the Retina, Nord. med. **46**:1422, 1951. (*o*) Barber, A. N.; Brauer, R. W., and Muelling, R. J., Jr.: Studies on the Effects of Beta Irradiation Applied Circumferentially to the Ciliary Body of Rabbits, Am. J. Ophth. **34**:175, (May Pt. 2) 1951. (*p*) Paufique, L.; Papillon, J., and Guinet, P.: Roentgen Therapy of Edematous Exophthalmos Without Hyperthyroidism, J. radiol. et. electrol. **32**:21, 1951. (*q*) Salerno, P. R.; Mattis, P. A., and Friedell, H. L.: Administration of Pharmacological Agents as a Protective Measure Against Lethal Effects of X-Irradiation in Mice, Federation Proc. **11**:387, 1952. (*r*) Burnett, W. T., Jr.; Stapleton, G. E.; Morse, M. L., and Hollaender, A.: Reduction of X-Ray Sensitivity of Escherichia Coli B/r by Sulfhydryl Compounds, Alcohols, Glycols, and Sodium Hydrosulfite, Proc. Soc. Exper. Biol. & Med. **77**:636, 1951. (*s*) Kahn, J. B., Jr.: Modification of Sensitivity to X-Irradiation by Morphine Sulfate, ibid. **78**:486, 1951. (*t*) Jacobson, L. O., and Robson, M. J.: Factors

than the less active cells. Blood cells are particularly vulnerable to radiation. The lymphoid tissues, lymph nodes, spleen, and tonsils, which produce and store white blood cells, are easily damaged. Thus, by damaging the white cells, one predisposes the body to infection. The bone marrow, the sex glands, the skin, the gastrointestinal tract, and the walls of blood vessels also suffer from radiation. The method by which radiation produces these effects in the body is not known. It is not known whether its action on the tissues is direct, causing a break-up and destruction of the cells, or indirect, such as the conversion of body substances into poisons or the release of poisons from the injured cells.

Basic studies to date have concerned themselves with the effects of radiation on the cells. It has been shown that the cells may be affected in many ways. They may be killed outright. Radiation may inhibit the growth; it may change the genes, and thus heredity. For many years studies have demonstrated by experiments on bacteria and fungi, and on seeds, that many cells are killed, that many types of genetic mutations are produced, that respiration may be inhibited, and that cell division may be interfered with, to produce variations, such as abnormally large cells. It is probable that radiation has its effects through its ionizing action on the atoms and molecules of which the cell is composed. Any radiation whether in the form of x-rays or gamma rays, or of neutrons or beta particles, ionizes the atoms among which it passes; that is, it removes an electron from a neutral atom, creating a positive ion, and the released electron then joins another atom to form a negative ion. This is not a selective process. Radiation ionizes impartially any atom or molecule in its path, whether it is water, a protein, an enzyme, a hormone, or any other substance. The ionization may change the molecule in a very important way, making it a great deal more active chemically. Since water is the main constituent of most cells, it is most likely to be ionized. Radiation removes an electron from the water molecule, forming a positive H_2O ion. The H_2O^+ ion then breaks down into H^+ and OH. The free electron may become attached to another water molecule and form a negative H_2O ion, which, in turn, breaks into H and OH^-. The ionization of water may thus yield four powerful oxidizing agents: H_2O_2, O, and the free radicals OH and HO_2. These agents can oxidize substances in the cell and thus interefere with its normal chemical reaction (Figs. 7, 8, and 9, reproduced from Spoerl.[179a]).

It has been shown by E. S. G. Barron, of the University of Chicago, cited by Spoerl,[179a] that the oxidizing agents may inactivate enzymes, thereby disturbing the metabolism of the cell. The enzyme protein molecule contains sulfhydryl groups, and it is known that many enzymes cannnot function if these groups are oxidized or changed. Barron suggests that these sulfhydryl groups are oxidized, and thus inactivated. Barron's studies have shown that irradiation will

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Affecting X-Ray Inhibition of Antibody Formation, J. Lab. & Clin. Med. **39**:169, 1952. (*u*) Burn, J. H.; Kordik, P., and Mole, R. H.: The Effect of X-Irradiation on the Response of the Intestine to Acetyl Choline and on Its Content of Pseudo-Cholinesterase, Brit. J. Pharmacol. **7**:58, 1952. (*v*) Anderson, C. T.; Blaschko, H.; Burn, J. H., and Mole, R. H.: Influence of X-Irradiation on Response of the Intestine, ibid. **6**:342, 1951. (*w*) Roberts, J. E.: Some Clinical Applications of Radioactive Isotopes, Arch. Middlesex Hosp. **1**:219, 1951. (*x*) Mitchell, J. S.: Practical Aspects of Radioactive Isotopes in Relation to Medical Treatment, Brit. M. J. **2**:747, 1951. (*y*) Wormall, A.: Theoretical Aspects of Isotopes in Relation to Medicine, ibid. **2**:757, 1951. (*z*) Duffy, B. F., Jr., and Howland, J. W.: Radiophosphorus (P-32) in Diagnosis and Treatment, New York J. Med. **52**:551, 1952. (*a'*) Thomas, C. I.; Krohmer, J. S., and Storaasli, J. P.: Detection of Intraocular Tumors with Radioactive Phosphorus, A. M. A. Arch. Ophth. **47**:276, 1952. (*b'*) Eisenberg, J.; Sklaroff, D.; Leopold, I. H., and Hallett, J.: Radioactive Isotopes in the Differential Diagnosis of Intraocular Tumors, read before the Monthly Wills Hospital Conference, February, 1952. (*c'*) Chou, S. N.; Aust, J. B.; Moore, G. E., and Payton, W. P.: Radioactive Iodinated Human Serum Albumin as Tracer Agent for Diagnosing and Localizing Intracranial Lesions, Proc. Soc. Exper. Biol. & Med. **77**:193, 1951. (*d'*) Moore, G. E.; Caudill, C. M.; Marvin, J. F., and others: Clinical and Experimental Studies of Intracranial Tumors with Fluorescein Dyes: With an Additional Note Concerning the Possible Use of K^{42} and Iodine 133 Tagged Human Albumin, Am. J. Roentgenol. **66**:1, 1951.

cause oxidation of these compounds. Various kinds of radiation—x-rays, and alpha, beta, and gamma rays—all inactivated these enzymes. However, they have also shown that these enzymes can be reactivated by the addition to the solution of a compound, such as glutathione, which supplies sulfhydryl groups. However, this was possible only when the enzymes received only moderate doses of radiation. After large doses the enzymes could be reactivated only partially, and usually not at all. Thus it appears that radiation damages or kills cells mainly by an indirect process. Irradiation ionizes water to form oxidizing agents. The oxidizers inactivate enzymes. This inactivation, in turn, damages the cell. However, it is not yet certain that this is a major means by which radiation attacks the living cell. It might disrupt the protein directly by breaking the chemical bonds of the molecule, or it might change the nuclear material. It has been shown by von Sallmann and Munoz [179k] that cysteine protects the lens from certain damages produced by x-rays, whether the cysteine is administered locally, by subconjunctival injection, or systemically, by intravenous injection. They obtained better results by intravenous administration. It has also been shown that these agents will protect the lens epithelium, there being less evidence of x-ray-induced cell death in the peripheral zone in the cysteine-pretreated eyes. There were less displacement of individual nuclei in the epithelial cells of the lens in the pretreated eye and less nuclear fragmentation, with extrusion of Feulgen-postive material. When four sulfur-containing compounds and four sulfur-free compounds were

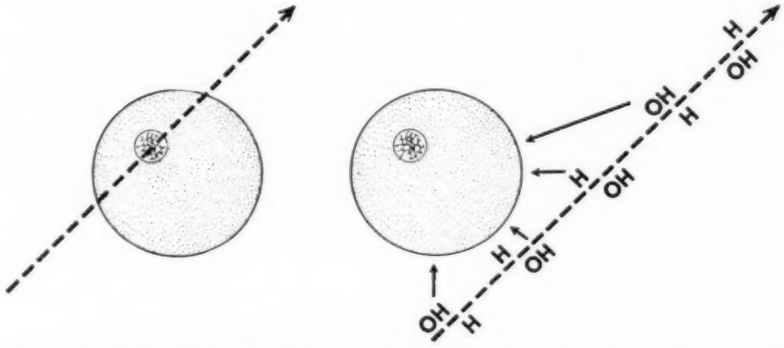

Fig. 7.—Effect on the cell can be direct or indirect. The radiation (dotted line) can damage the cell by passing through it (left) or by manufacturing reactive groups of atoms that pass through the cell wall (right). Reprinted, with permission, from Spoerl.[179a]

tried for their protective effects, the sulfur-containing compounds being glutathione, thiourea, sodium thioglycollate, and dimercaprol, and the sulfur-free compounds, dihydroxyacetone, *d*-alpha-tocopherol, citrovorum factor (folinic acid), and potassium cyanide, only glutathione and thiourea exerted a beneficial effect on the x-irradiated eyes. However, most of these substances had been shown to be effective in protecting bacteria or mice against the lethal action of x-rays. Therefore it is apparent the results obtained on such material cannot be applied directly to the eye so far as the protective action on the lens is concerned.

It has been suggested that radiation causes mutation of genes in the cell nucleus by some kind of direct action, perhaps by striking the large gene molecule. It has been shown that rats can survive much larger doses of radiation if their oxygen supply is reduced below normal. These experiments again indicate that the radiation works indirectly; and the findings that the amount of oxygen present influences the effect of radiation on chromosome aberrations suggests that the effect on the genes is an indirect one. Evidence is also available suggesting that radiation operates indirectly on divisions of cells through a chemical mechanism. It has been shown that cells which are actively growing and dividing contain more sulfhydryl groups than do resting cells. It appears, therefore, that radiation could stop the division of cells by oxidizing the sulfhydryl groups. There is also evidence that it can interfere by striking the desoxypento-nucleic acid in the nucleus of the cells. Thus, it is now evident that oxidation plays an important

part in radiation damage. This damage may be brought about through the ionization of water, resulting in a formation of oxidizing agents; and this mechanism may be the chief means by which radiation injures cells.

Von Sallmann's studies [179k] along this line add support showing that the addition of a sulfhydryl-supplying substance, such as cysteine or glutathione, is helpful. However, it should be noted, as von Sallmann has stressed, that in the animal experiments these additional materials have not been effective as treatment, but that they protect the animal only if they are present prior to the irradiation. Thus, it appears that we must learn more about cell metabolism and cell functions if we are to be able better to handle the effects of radiation.[179a]

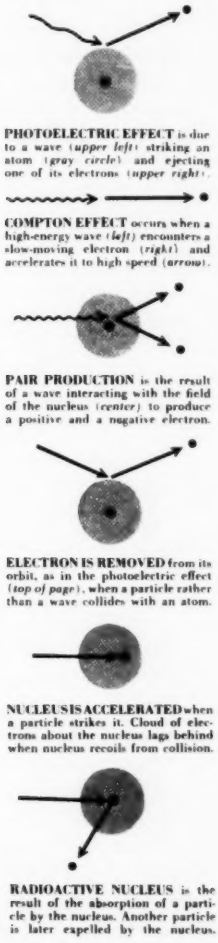
PHOTOELECTRIC EFFECT is due to a wave (upper left) striking an atom (gray circle) and ejecting one of its electrons (upper right).
COMPTON EFFECT occurs when a high-energy wave (left) encounters a slow-moving electron (right) and accelerates it to high speed (arrow).
PAIR PRODUCTION is the result of a wave interacting with the field of the nucleus (center) to produce a positive and a negative electron.
ELECTRON IS REMOVED from its orbit, as in the photoelectric effect (top of page), when a particle rather than a wave collides with an atom.
NUCLEUS IS ACCELERATED when a particle strikes it. Cloud of electrons about the nucleus lags behind when nucleus recoils from collision.
RADIOACTIVE NUCLEUS is the result of the absorption of a particle by the nucleus. Another particle is later expelled by the nucleus.

Fig. 8.—Reprinted, with permission, from Spoerl.[179a]

When slow neutron radiation heavily contaminated with gamma rays was directed to the entire body of mice, cataracts developed which were similar to those seen after exposure to x-irradiation. The neutron radiation induced changes more quickly than x-rays in mice at a lower dosage level, on the basis of a half-lethal dose. Mice appeared to be much more susceptible to radiation cataract than was man.[179d]

In attempting to correlate radiation cataracts with other manifestations of x-irradiation in and about the eye, Cogan and Donaldson [179e] found that epilation

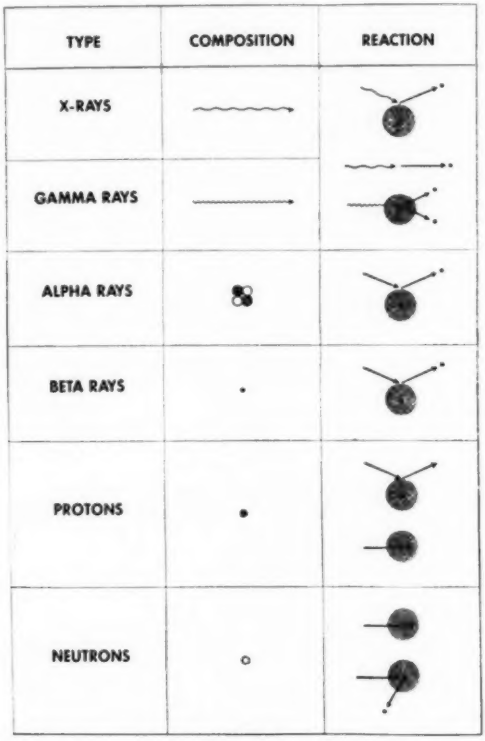

Fig. 9.—Physical effects of various radiations on the atoms of living things are outlined in this chart. The electromagnetic radiations are indicated by wavy lines. The alpha particle is made up of two protons and two neutrons.

occurred in 15 to 35 days with doses of 1,500 r or greater, coming on sooner and being more profound the larger the dose and the less the energy of the x-rays. The threshold dose for epilation was 1,500 r for the 1,000-kv. level and 1,000 r for the 200-kv. level. Little variation of susceptibility was found with age. The same generalization may be applied to keratoconjunctivitis.

The latent period was an inverse function to the dose. Moreover, the younger the rabbit, the shorter the latent period. With x-ray doses of less than 1,000 r, cataract was the only

abnormality produced. Radiation cataract in the rabbit began with aggregation of vacuoles along the posterior suture line, oftenest at either extremity; granular opacities, either scattered about the suture line or arranged in ring fashion in the paracentral region, and an equatorial collaret beneath the posterior capsule. The granules which were found about the suture were due to epithelial cells which, instead of forming fibers at the equator, had migrated posteriorly. Characteristic cytologic changes in the lens epithelium could be noted after irradiation. These consisted of a spotty occurrence of cells having several times the normal complement of cytoplasm and of nuclear fragmentation, varying from mere budding to frank karyorrhexis.

Cogan and his co-workers [179f] present the histologic changes in 27 cases of radiation cataract. These changes appear first as a doughnut-shaped configuration, as seen with the ophthalmoscope. The sharply demarcated anterior border of the opacity and the bivalvular configuration of the opacity are seen with the slit-lamp biomicroscope. These are not observed in all stages of radiation cataract and are not found exclusively in radiation cataract, but are strongly suggestive evidence of this type. The histologic changes consist primarily of failure of the cells at the equator to differentiate into lens fibers and of the early migration of cells beneath the posterior capsule toward the posterior pole. These aberrant cells may cause thickening of the capsule and undergo changes that are interpreted as abortive attempts at differentiation of lens fibers. Thus, the histologic changes are less specific than the clinical ones.

Radiation cataract is a late effect of exposure to the atomic bomb that has appeared among the more heavily irradiated survivors in Hiroshima city and Nagasaka city, Japan. Clinically this cataract is similar in appearance to the cataract produced by x-rays and radium and exhibits fairly definite characteristics. A posterior polar opacity develops which has fairly sharp borders, both anteriorly and equatorially. It lies in the subcapsular region and appears as a lace-like disk containing small vacuoles. So-called complicated cataract differs from radiation cataract in that it is diffuse, flocculent, and not sharply defined from the rest of the lens.[179g-i]

Von Sallmann and co-workers [179j, k] have demonstrated that the exposure of the rabbit eye to the beam of x-rays, 1,500 r, was followed by almost complete disappearance of dividing cells in the lens epithelium 30 minutes after irradiation. This total inhibition lasted from three to four days. Recovery of mitosis took place in the next four days and was followed by a period of overcompensating increase in the proportion of dividing cells, which could be observed for at least one week. Nuclear fragmentation began two hours after irradiation, and there was a steep rise in incidence of this sign of radiation injury when the inhibition of mitosis terminated, particularly when the overshooting phenomenon had fully developed. A relative depletion of cell elements, most striking in the equatorial zone, was considered a result of this nuclear fragmentation, which led characteristically to a liquefaction of cell bodies with vacuole formation. Cysteine treatment of irradiated animals prolonged the inhibitory effect of x-rays on mitosis, slowed the speed of recovery, and reduced the extent of overshooting and cell division, particularly when cysteine was injected prior to the exposure of the eye to a dose of 1,500 r. The relative protective action of pretreatment with cysteine against x-ray damage to the lens was demonstrated in this study by a lower incidence of nuclear fragmentation in all zones

of cysteine-pretreated eyes as compared with the incidence of this type of damage in the eyes of untreated irradiated rabbits and the eyes of rabbits treated after irradiation.

Von Sallmann and co-workers [179j-k] have shown that cysteine and cystine penetrate readily from the blood into the aqueous humor. The highest levels were obtained after intravenous injection and occurred one hour after injection. The authors present evidence that the oxidation of cysteine to cystine progressed at a high rate in the aqueous humor. Cystein protected the lens and the lids from the effects of a single dose of 1,500 r of x-rays when injected intravenously prior to irradiation, but was ineffective when administered shortly after the exposure. Cysteine administered by iontophoresis or by intraperitoneal injection did not appear to have this protective action.[179j, k]

Other investigators have shown a similar protective action in human skin.[1791]

In children subjected to cranial x-ray therapy for ringworm, there were subjective dimming of vision, without objective decrease of visual acuity, and temporary dilatation of retinal veins. These manifestations appeared after the second application. The dose employed was 410 to 420 r at each application.[179m]

Ganglionic cells in the retina react like other motor and sensory cells after exposure to x-rays.[179n]

Working on the postulate that a decrease in production of aqueous humor and a lower intraocular pressure might follow reduction of the capillaries in the ciliary body, Barber and co-workers applied beta radiation in the form of 10 mc. of P^{32} circumferentially, to the ciliary body of rabbits three to six times during a period of three months.

> The period of application varied from 5 to 10 minutes, and the total time of application was 15 to 40 minutes. In none of the rabbits was there any gross or microscopic evidence of cataract formation. Evidence obtained of a reduction in intraocular pressure and a decrease in vascularity of the eye so treated. It would appear, as has previously been reported, that after beta irradiation the vascular endothelium is not damaged, but that the chief change in the ciliary body was a compactness of the stroma, with obliteration of some of the intrastromal capillaries.[179o]

Paufique and co-workers [179p] report benefit in cases of exophthalmos without hyperthyroidism from a combined course of x-rays and panhormonal therapy, thyroxin and estrogens being used mainly. It was the treatment of choice in all but the milder cases of recent onset, in which hormonal therapy alone may suffice.

Numerous agents have been examined for their protective effect against radiation damage. A number, such as alcohols, glycols [179q, r] and morphine,[179s] have shown beneficial protective action. Lowered oxygen tension has been shown to prevent damage from x-rays in a variety of organisms. Artificially produced anoxia has been shown to protect animals from the lethal effects of x-rays to some extent. Morphine, because of its depressive action on the respiratory center, was tried in this connection. It was found that morphine injected intramuscularly into mice 30 minutes before exposure of the entire body to x-rays raised the lethal dose from 609 to 803 r. The beneficial effect may be explained by one of the following mechanisms: Morphine has a hyperglycemic effect. It is known that some species of organisms can be protected from the lethal effect of x-rays by intraperitoneal injection of dextrose. This explanation, however, is probably not valid. It is more probable that morphine depresses the respiratory center, producing anoxia and methemoglobinemia in some of the radiosensitive tissues.

X-irradiation may inhibit antibody formation, but this can be prevented by shielding of the spleen.[179t]

In an effort to explain the action of x-rays on the intestinal tract, studies were made of the cholinesterase content. It was found that irradiation produced a fall in concentraion of pseudocholineserase, but not in that of the true, or specific, cholinesterase.[179u,v]

Radioactive isotopes continue to receive considerable attention in medicine.[179w-b'] They have been used in estimation of the volume of body fluids, in determination of thyroid functon in the therapy of thyroid disease, in the treatment of blood disorders, and in the localization of tumors. Radioactive phosphorus has received further attention during the past year for localization of intracranial neoplasms,[179x-z] most recently, as reported by Thomas and his co-workers,[179a'] in the detection of intraocular tumors. This method may prove an important aid in the differential diagnosis of intraocular tumor.[179a'] Personal experience with the use of radioactive diiodofluorescein and a scintillation counter have proved in a small series to be inadequate for differential diagnosis of intraocular neoplasms. However, studies with radioactive phosphorus have been more encouraging.[179b'] Other radioactive agents, such as potassium and iodinated human albumin, may be helpful in this regard.[179c',d]

Radioautography.—Radioactive isotopes have been used for measurement of turnover rates, the concentration of isotope in animal carcass, and the concentration in individual organs or in organ extracts. Recently they have been used to study cellular function at the cell level.

Radioautography, or autoradiography, consists in placing organisms, histologic sections, smears, or objects containing radioactive isotopes adjacent to photographic emulsion and recording in the reduced metallic silver of the emulsion an image of the radioactive areas of the object.[180] This is possible because of the faculty of the alpha particles, beta particles, or gamma rays given off by the isotope to reduce photographic emulsions in a manner similar to light.

By this means, mustard gas containing radioactive sulfur has been localized in the eyes of rabbits after exposure to the gas vapor. Five minutes after exposure the isotope could be found in the cornea, iris, and ciliary body; seven days later it was found only in the cornea. Von Sallmann, cited by Fitzgerald,[180a] used this method to study the distribution of I^{132} and Na^{24} in rabbit eyes. Palm, also cited by Fitzgerald, [180a] studied the distribution of P^{32} in the eyes with this technique. Using such a technique, Kass [182] studied the effects in vitro of radioactive I^{132} and labeled 3,5-diiodoparaaminosalicylic acid on the tubercle bacillus. Neither potassium iodide nor radioactive I^{131} had any tuberculostatic effectiveness. Although I^{131} has no effect, radioactive I^{131} labeled 3,5-diiodoparaaminosalicylic acid was shown to have a positive uptake in the tubercle bacillus.

Schurr [183] calls attention to the potential value of angiography for visualization of the ophthalmic artery and choroidal plexus. Falls and his co-workers [184] call attention to the ocular complications of angiography.

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180. (*a*) Fitzgerald, P. J.: Radioautography in Cancer, Cancer **5**:166, 1952. (*b*) Mayneord, W. V.: Radiography of the Human Body with Radioactive Isotopes, Lancet **1**:276, 1952.

181. Footnote deleted.

182. Kass, I.: Studies on the in Vitro Effects of Radioactive I-131 Labeled 3,5 Diiodoparaminosalicylic Acid on the Tubercle Bacillus. Am. Rev. Tuberc. **65**:316, 1952.

183. Schurr, P. H.: Angiography of the Normal Ophthalmic Artery and Choroidal Plexus of the Eye, Brit. J. Ophth. **35**:473, 1951.

184. Falls, H. F.; Bassett, R. C., and Lamberts, A. E.: Ocular Complications Encountered in Intracranial Arteriography, A. M. A. Arch. Ophth. **45**:623, 1951.

Twenty-seven patients with sympathetic ophthalmia, clinically diagnosed but not histologically confirmed in all cases, were found to respond favorably to x-ray therapy with stimulating doses ranging from 100 to 150 r each time, up to a total of 700 r.[185]

Supersonics.—Supersonic waves have been tried in the therapy of ocular diseases, such as hemorrhage in the vitreous, but the value of this form of therapy is doubtful.[186]

Repeated treatment of the rabbit eye with a dose of 2 watts per square centimeter for three minutes with a water electrode applied directly to the eye increased the permeability of the intraocular vessels. This effect lasted two hours. Treatment of one eye caused reflex vasodilation in the other eye. Supersonic treatment of the cervical sympathetic fibers altered the blood-aqueous barrier. The fact that supersonic waves liquefy the vitreous and the present difficulties of standardizing the apparatus are drawbacks to clinical trial.[187]

With low-frequency, high-intensity supersonic beams, a reversible type of fine perinuclear opacities can be produced in the lens. These opacities are thought to be the result of cavitation. Another type of irreversible cataract is thought to be due to absorption of high-frequency, high-intensity supersonic radiation, which results in high local temperatures. It has also been shown that the vitreous can be liquefied by supersonic radiation and that this is irreversible.[188]

TISSUE THERAPY

The present status of tissue therapy in ophthalmology is still uncertain. Some investigators claim pronounced improvement following its use; others claim that it is best only as an adjuvant form of treatment; still others think that it has no value.[189]

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185. di Luca, G.: Observations of Sympathetic Ophthalmitis from the Clinical and Therapeutic Point of View with Special Reference to X-Ray Therapy, Boll. ocul. **33**:54, 1951.

186. (*a*) Belz and Bouchel: Ultrasound Therapy in Hemorrhage of the Vitreous, Lyon Med. **184**:187, 1951. (*b*) Belz: Ultrasonics in Ophthalmology, Ann. ocul. **184**:673, 1951.

187. (*a*) Hallermann, W.; Basch, A., and Ladeburg, H.: The Effect of Ultrasonic Waves on the Animal Eye, Klin. Monatsbl. Augenh. **119**:401, 1951. (*b*) Krusen, H.: Present Status of the Use of Ultrasonic Energy in Physical Medicine, South. M. J. **45**:55, 1952.

188. Lavine, C.; Langenstrass, K. H.; Bowyer, C. M.; Fox, S. E.; Griffin, G. B., and Thaler, W.: Effect of Ultrasonic Waves on the Refractive Media of the Eye, A. M. A. Arch. Ophth. **47**:204, 1952.

189. (*a*) Barraquer-Moner, J. I.: The Present State of Tissue Therapy in Ophthalmology, Arch. soc. oftal. hispano-am. **11**:837, 1951. (*b*) Lijó Pavia, J., and Arouh, J.: Biogeno-Therapy in Ophthalmology, Rev. oto-neuro-oftal. **26**:73, 1951. (*c*) Arouh, J., and Lijó Pavia, J.: Biogenic Treatment in Ophthalmology, Arch. oftal. Buenos Aires **26**:131, 1951. (*d*) Karaz, Z.: Tissue Therapy in Ophthalmology, Oto-neuro-oftal. **6**:42, 1951. (*e*) Kriz, R.: Our Experience with Placental Extract, Českoslov. Ofth. **7**:105, 1951. (*f*) Wei, C. H.; Pai, H. L., and Yamazaki: Final Report on Cases Treated with Tissue Therapy, Chinese J. Ophth. **1**:184, 1951. (*g*) LeGrand, J.: Limitations of Tissue Therapy, Bull. Soc. opht. France **1**:92, 1951. (*h*) LeGroux, R.: Acute Hypertony After Placental Implantations in a Case of Retinitis Pigmentosa, ibid. **1**:46, 1951; (*i*) Placental Implants: Therapeutic Results, ibid. **1**:47, 1951. (*j*) Oudot, N.: Tissue Therapy in Some Cases of Severe Keratitis, ibid. **1**:88, 1951. (*k*) Macki, E. G.: Placental Implantations for Retinitis Pigmentosa, Proc. Soc. Med. **44**:977, 1951. (*l*) Bourdier, F.: The Use of Reticuloendothelial Sero-Therapy in Ophthalmology, Ann. ocul. **184**:769, 1951. (*m*) Azzolini, U., and Faldi, S.: Oidiumycine-101 in Ocular Therapy, Arch. ottal. **55**:285, 1951. (*n*) Granirer, L. W.: Clinical Response of Rheumatoid Arthritis to Postpartum Plasma: A Two-Year Study, J. A. M. A. **146**:995, 1951. (*o*) Dillon, R. N., and Majnarich, J. J.: Placental Extract in Treatment of Rheumatoid Arthritis, Northwest Med. **56**:77, 1951. (*p*) Stewart, H. L., Jr.: Hormone Secretion by Human Placenta Grown in the Eyes of Rabbits, Am. J. Obst. & Gynec. **61**:990, 1951. (*q*) Gaba, V.; Skacel, J., and Sabata, J.: Treatment of Eye Diseases with Refrigerated Autogenous Blood, Českoslov. ofth. **7**:271, 1951.

Bourdier [189l] has used Bogomoletz' reticuloendothelial serum. He compares the use of this serum with Filatov's tissue therapy and describes the reticuloendothelial system as being similar in action to a vaccine, while Filatov's tissue and serum extract corresponds to an antitoxin. He believes that the retinal arterial pressure is affected by injection, sometimes being increased, sometimes lowered; but the tendency is always toward regularization. No definite conclusions can be drawn from the study.

Oidiumycine-101 is supposedly a catalyst and a biologic stimulant. When introduced subconjunctivally or parenterally, it may be effective in a variety of inflammatory ocular conditions of chronic nature.[189m]

Additional evidence has been presented that the placenta is an organ of internal secretion,[190] possessing corticotropin, as well as other hormones. This is of particular interest in view of the long-standing data of Filatov and other foreign investigators, who use placental extracts and placental implant in the treatment of a variety of ocular diseases, with beneficial results reported. Pieces of full-term human placenta were implanted in the anterior chambers of rabbit eyes, and the effects were observed from four to six months. It was found that Langhans cells grew and that large follicles, corpora hemorrhagica, and corpora lutea developed in the ovaries. This proved that Langhans cells are present in the human placenta at term and that they produce chorionic gonadotropin. In further experiments, full-term placental tissue was implanted into the eyes of castrated rabbits. The uterus enlarged, with evidence of estrogenic development, but, with one exception, without any evidence of progestational change.[189p]

ANESTHESIA

Intravenous Injection of Morphine.—Johnson [191] reports on 101 cases in which morphine was used intravenously.

The preparation that he employed contained morphine sulfate, ¼ grain (15 mg.); ephedrine sulfate, ⅙ grain (10 mg.), and scopolamine hydrobromide, 1/200 grain (0.30 mg.), with chlorobutanol, 0.5%. All these ingredients were dissolved under aseptic conditions in 4 mm. of triple-distilled water. Premedication consisted in administration of amobarbital (amytal®) sodium, 3 grains (0.20 gm.) before retiring and repeated two hours before operation. The morphine solution was injected slowly, at approximately 1 ml. in two minutes. The maximum depressive effect occurred in 7 to 10 minutes; the maximum psychic sedative effect, in 10 minutes, and the maximum analgesic effect, in 20 minutes. There was a striking absence of side-effects except for dizziness in two patients, tachycardia in two patients, and respiratory depression with mild cyanosis in three patients. Postoperative incidents of nausea and headache were mild and occurred in less than 10% of patients.[191]

Curare and Anesthetics in Ocular Surgery.—Curare continues to be reported on by numerous ophthalmologists who find it of definite value in obtaining better relaxation of the extraocular muscles and in reducing loss of vitreous during cataract extraction. Most workers believe that the curare should be given only by the anesthetist, who uses his judgment as to the amount and the time of injection. The

190. Opsahl, Long, and Fry.[65e] Tarantino.[101w] Opsahl and Long.[101y] Pelloja.[101z] Granirer.[189n] Dillon and Majnarich.[189o] Stewart.[189p]

191. Johnson, E. A.: Intravenous Morphine in Ocular Surgery, Canad. M. A. J. **64**:429, 1951.

anesthetist should be familiar both with the drug and with the surgical procedure on the eye.[192]

According to Farquharson,[192a] neostigmine does not deserve a place in the management of curare overdosage.

If curare is carefully administered, there should be no overdosage, and any untoward effects are so transient that they may be dealt with by reassurance of the patient and administration of oxygen by mask. Pure oxygen, with or without artificial respiration, was not required by either Farquharson [192a] or Cordes and Mullen [192b] in their series. Patients who had previously undergone cataract extraction on the other eye without curare commented favorably on the effect of the drug when it was used for their second eye operation. They stated that they were relaxed and had no fear that they would move during a crucial stage of the procedure. However, it is necessary to warn the patient not to breathe deeply. He should try to keep his respiration at a minimum. Otherwise, he may become alarmed at his inability to perform such deep-breathing movements.

In search for a better anesthesia for the office examination of infants and young children, trichloroethylene was studied and is recommended.[193]

Trichloroethylene, a chlorinated hydrocarbon, has an odor similar to that of chloroform. Its formula is CCl_2CHCl. It has to be stored in a colored bottle, as it decomposes in strong sunlight. It is insoluble in water. It is thought to act by its absorption into the blood stream and its subsequent effect on the central nervous system. Trichloroethylene is self-administered by the patient, and it serves to relieve the pain and anxiety when one is giving an injection for akinesia or during an operation on the skin done with analgesia.

Leffingwell [194] and Deming [195] point out that one should not be indifferent to the use of general anesthesia for minor office procedures. They believe that there is no such thing as a minor anesthetic procedure. The degree of security involved in any anesthetist's work is entirely dependent on the equipment he uses, the knowledge he possesses, and the practices he follows. One should have a thorough knowledge of the agent that is being used and should be prepared for any emergency that may result by virtue of the use of the anesthetic.

Local Anesthetics.—Local anesthetics may be classified as follows [196]:

1. Cocaine group: cocaine, cocaine tartrate ("psicain"), tropacocaine (benzoylpseudotropine)
2. Procaine group: derivatives of benzoic acid
   (*a*) procaine, (tetracaine) (pontocaine®), butacaine, butethamine (monocaine®)
   (*b*) More complicated derivatives of benzoic acid
   Piperocaine (metycaine®), amylocaine (stovaine®)
   (*c*) Insoluble compounds of benzoic acid
   Ethyl aminobenzoate ("benzocaine"), orthocaine BF.
3. Phenol carbinols: benzyl alcohol, saligenin (salicyl alcohol)
4. Mixed group: dibucaine (nupercaine®), phenacaine N.F.

192. (*a*) Farquharson, H.: Curare with Local Anesthesia in Cataract Surgery, Am. J. Ophth. **34**:554, 1951. (*b*) Cordes, F. C., and Mullen, R. S.: The Use of Curare in Cataract Surgery, ibid. **34**:557, 1951. (*c*) Escuin Vera, J. M.: Curare: One Thousand Cases of Administration in Ocular Surgery, Día méd. **23**:64, 1951. (*d*) Barraquer Moner, J.: Curare in Ocular Surgery, Presse méd. **59**:1078, 1951. (*e*) Curare in Ophthalmic Surgery, Arch. Soc. oftal. hispano-am. **11**:683, 1951. (*f*) Patterson, R. L.: The Use of Muscle Relaxing Drugs in Anesthesia, Anesth. & Analg. **31**:65, 1952.

193. Offenbach, B.: Trichlorethylene as an Analgesic in Ophthalmic Practice, Am. J. Ophth. **35**:250, 1952. Scharf, J., and Grethe, H.: The Use of Trichlorethylene for Inhalation Analgesia in Ophthalmology, Klin. Monatsbl. Augenh. **119**:49, 1951.

194. Leffingwell, F. E.: Office Practice of Anesthesia, J. A. M. A. **148**:1181, 1952.

195. Deming, M. N.: Agents and Techniques for Induction of Anesthesia in Infants and Young Children, Anesth. & Analg. **31**:113, 1952.

196. Good, M. G.: Theory of Local Anesthesia, Anesth. & Analg. **31**:120, 1952.

A desirable local anesthetic should be easy to sterilize; should be completely soluble in cold isotonic sodium chloride solution in such concentrations as actually are used for induction of regional anesthesia; should allow complete and rapid absorption locally, leaving no trace of its passage at the site of injection; should have low toxicity in doses required to produce surgical anesthesia; should work rapidly, and should not be irritating. Tetracaine has many advantages for regional procedures.[197] It is not quite as rapid, however, as procaine in its onset of analgesia when used in very dilute concentration. Undesirable reactions to tetracaine are not common, according to Moore.[197a] They are characterized by drowsiness, shallow respirations, and apnea. Reactions should be combated with oxygen therapy only unless the blood pressure falls, when vasoconstrictor agents can be employed; and if convulsions are present and sustained or repeated, a barbiturate can be administered intravenously. Tetracaine gives a minimum of five hours of anesthesia when used for nerve block and local infiltration. Postoperative analgesia lasts from four to nine hours. This is of the utmost importance in reducing postoperative complications and instituting early ambulation.

Since any anesthetic agent is potentially toxic, the physician must be able to recognize and cope with untoward reactions. Not sensitivity, but overdosage, is responsible for most untoward effects of local anesthesia. Too rapid injection, rapid absorption from a highly vascular site, or inadvertent entry of a vessel may be responsible for adverse reactions. There may be a stimulatory effect on the central nervous system, causing anxiety, nervousness, tremors, or even convulsions. As a precautionary measure, short-acting barbiturates should be injected intramuscularly about two hours before anesthesia. Central nervous depression is always preceded or accompanied by some stimulation, however brief and slight; speech fails; voluntary muscles relax, and breathing may cease. There may be central vasomotor depression. Of the abnormal responses, allergic forms are primarily cutaneous eruptions, such as hives or angioneurotic edema; contact dermatitis may result from anesthetic ointment.[198]

Comparison of Procaine and Lidocaine (Xylocaine).—Procaine and lidocaine produced effective degrees of nerve-block anesthesia in 2% concentration. Anesthesia was slower in onset, shorter in duration, and less uniformly complete after procaine.[199] Procaine amide has certain advantages over procaine in anesthesia. It has a much more prolonged action, and it can be administered orally.[200]

The New Anesthetics.—An isoquinoline compound, "quotane" (1-[B-dimethylaminoethoxy]-3-N-hitylisoquinoline monohydrochloride) was 1,000 times as active

197. (*a*) Moore, D. C.: Pontocaine Solutions for Regional Analgesia Other Than Spinal and Epidural Block, J. A. M. A. **146**:803, 1951. (*b*) Bonica, J. J.: Use of Pontocaine for Regional Anesthesia, Anesth. & Analg. **30**:76, 1951.

198. Sadove, M. S.; Wyant, G. M.; Gittelson, L. A., and Kretchmer, H. E.: Classification and Management of Reactions to Local Anesthesic Agents, J. A. M. A. **148**:17, 1952. Ludenna, F. P., and Hoppe, J. O.: Local Anesthetic Activity, Toxicity and Irritancy of 2-Alkoxy Analogs of Procaine and Tetracaine, J. Pharmacol. & Exper. Therap. **104**:40, 1952. Thiel, R.: Corneal Injury Through Misuse of Analgesics, Deutsche med. Wchnschr. **76**:278, 1951. Lane, C. G., and Luikart, R.: Dermatitis from Local Anesthetics, J. A. M. A. **146**:717, 1951. Weisel, W., and Tela, R. A.: Reaction to Tetracaine (Pontocaine) Used as a Topical Anesthetic in Bronchoscopy, ibid. **147**:218, 1951. Ireland, P. E.; Fergusson, J. K. W., and Stark, E. G.: Clinical and Experimental Comparison of Cocaine and Pontocaine as Topical Anesthetics in Otolaryngological Practice, Laryngoscope **61**:767, 1951. Young, P. A.: Duration of Cocaine Anesthesia in the Rabbit Cornea, Brit. J. Pharmacol. **60**:73, 1951.

199. Tullar, P. E.: Local Anesthetic Studies with Procaine and Xylocaine, Federation Proc. **11**:398, 1952.

200. Sadove, M. S.; Wynant, G. M.; Kretchmer, H. E., and Gittelson, L. A.: Procaine Amide: A Clinical Study, Anesth. & Analg. **31**:45, 1952.

as cocaine and 10 times as active as dibucaine. It was less toxic than dibucaine, but more toxic than cocaine. It was also 100 times as active as procaine. "Quotane" was used in concentrations of 0.01 to 0.1% and was compared with 1% cocaine and 0.1% dibucaine hydrochloride in these studies.[201] Xenon and krypton were also shown to have anesthetic properties.[202]

Relation of Cortisone, Desoxycorticosterone, and Corticotropin to Analgesic Drugs.—Cortisone and corticotropin reduced the effect of morphine and amidone ("methadone") on the central nervous system of rats. Cortisone increased the excitatory effect of morphine. Desoxycorticosterone had an opposite effect. In explanation of these actions, cortisone (1) might have an effect on the central nervous system the opposite of that of morphine; (2) might change the reactivity of cells of the central nervous system to morphine, or (3) might modify the effect by competitive inhibition. Since morphine and amidone are unlike chemically, the third possibility of competitive inhibition is unlikely.[203]

It has been mentioned previously in this review [170] that anticholinesterase agents when injected subconjunctivally produce local anesthesia.

It has been noted recently by Kalow [204] that there is in the tissues an enzyme which rapidly hydrolyzes procaine to a nontoxic product.

It may be that this enzyme, procainesterase, and serum cholinesterase may be identical, and Kalow's data certainly suggest this identity.[204] The inhibition of serum esterase action on acetylcholine by means of local anesthetics has been well established in the literature. Kalow demonstrated the converse, namely, that acetylcholine could inhibit procaine hydrolysis. Pseudocholinesterase splits procaine and other local anesthetics. Acetylcholine and procaine, or other local anesthetics, can act as competitive inhibitors of the same enzyme. Although the hydrolysis of acetylcholine is about 400 times as fast as that of procaine, the affinity of procaine for this esterase is about 200 times as great. Some correlation between the rate of hydrolysis and the duration of local anesthesia is apparent, particularly if procaine, tetracaine, and dibucaine are compared. The affinity of all local anesthetics investigated for serum cholinesterase is high. In the case of tetracaine, the affinity is of the same order of magnitude as that found for physostigmine.[204]

Stellate-Ganglion Block.—Stellate-ganglion block has been used for the therapy of retinitis pigmentosa [205] and for closure of retinal vessels.[206]

Kennedy and McGannon [205] conclude that stellate ganglionectomy and stellate-ganglion block are of no value in the treatment of retinitis pigmentosa. Pollin and Deutsch stress that the performance of stellate-ganglion block requires a thorough understanding of the anatomy and neurophysiology involved, and that the block should not be viewed as a simple procedure, to be performed by the untrained. They report a case of death following stellate-ganglion block and suggest the possible mechanism of death in this case as being due to vagal arrest of the heart and the central respiratory center.[207]

201. Fellows, E., and Mackoe, J. P.: Topical Anesthetic Activity of an Isoquinoline Compound, J. Pharmacol. & Exper. Therap. **103**:306, 1951.

202. Cullen, S. C., and Gross, E. G.: The Anesthetic Properties of Xenon in Animals and Human Beings with Additional Observations on Krypton, Science **113**:580, 1951.

203. Winter, C. A., and Flataker, L.: The Effect of Cortisone, Desoxycorticosterone and ACTH on the Response of Animals to Analgesic Drugs, J. Pharmacol. & Exper. Therap. **103**:93, 1951.

204. Kalow, W.: Hydrolysis of Local Anesthetics by Human Serum Cholinesterase, J. Pharmacol. & Exper. Therap. **104**:122, 1952.

205. Kennedy, R. J., and McGannon, W. J.: Stellate Ganglion Block in Retinitis Pigmentosa, A. M. A. Arch. Ophth. **47**:287, 1952.

206. Coston.[158] Scott.[159a] Leriche.[159b] Editorial.[159c]

207. Pollin, I. M., and Deutsch, E. V.: Death Following Stellate Ganglion Block, Ann. Surg. **133**:232, 1951.

Narcotics as Preanesthetic Agents.—Study of the narcotics as preanesthetic agents, by Cohen and Beecher,[208] suggested that pentobarbital sodium is an effective and satisfactory substitute for morphine in preanesthetic medication.

Both morphine and pentobarbital contributed little to the improvement of the patient's preanesthetic mental state and the induction of anesthesia. Both agents produced euphoria. This effect is desirable, but one difficult to measure exactly. Neither morphine nor pentobarbital contributed to reducing the actual blood levels of the anesthetic agents required to maintain surgical anesthesia. The authors did not mean to imply, however, that morphine is to be discarded entirely in preanesthetic medication. Rather, its use, and that of other powerful narcotics, should be restricted to providing analgesia. Patients in preoperative pain should receive an analgesic agent in preanesthesia medication, but few patients who come to operation have pain severe enough to require a narcotic.

HYPERTENSION

Therapy in Systemic Hypertension.—Many new drugs have been employed in the therapy of hypertension, such as the ganglion-blocking agents, hexamethonium iodide, and pentamethonium iodide, the cation exchange resins, veratrum viride, and betamine hydrate and glycocyamine. These forms of therapy and their general value have been summarized in Table 4.[209] The ganglion blocking agents, such as

208. Cohen, E. N., and Beecher, H. K.: Narcotics in Preanesthetic Medication, J. A. M. A. **147**:1664, 1951.

209. (*a*) Freis, E. D.: Veratrum Viride and Hexamethonium in the Treatment of Severe Diastolic Hypertension, M. Ann. District of Columbia **20**:297, 1951. (*b*) Schroeder, A. A.: Effects of (1) Hydrazinophthalozine in Neurogenic Hypertension, read before the 24th Scientific Sessions of the American Heart Association, Atlantic City, June 8, 1951. (*c*) Page, I. H.: Treatment of Essential Malignant Hypertension, J. A. M. A. **147**:1311, 1951. (*d*) Corcoran, A. C.; Taylor, R. D., and Page, I. H.: Controlled Observations on Effect of Low-Sodium Dieto-Therapy in Essential Hypertension, Circulation **3**:1, 1951. (*e*) Smirk, F. H.: Methonium Halides in High Blood Pressure, Science **114**:4, 1951. (*f*) Taylor, R. D.; Page, I. H., and Corcoran, A. C.: A Hormonal Neurogenic Vasopressor Mechanism, A. M. A. Arch. Int. Med. **88**:1, 1951. (*g*) Hormonal Cerebral Vasopressor Substance, editorial, J. A. M. A. **146**:1326, 1951. (*h*) Campbell, A. J. M.; Graham, J. G., and Maxwell, R. D. H.: Treatment of Hypertension by Oral Methonium Compounds, Brit. M. J. **1**:251, 1952. (*i*) Murphy, E. A.: Treatment of Hypertension with Hexamethonium Bromide, Lancet **2**:899, 1951. (*j*) Smirk, F. H., and Alstad, K. S.: Treatment of Arterial Hypertension by Penta- and Hexamethonium Salts, Brit. M. J. **1**:1217, 1951. (*k*) Peersson, I.: Treatment of Arterial Hypertension with Hexamethonium Bromide, Nord. med. **46**:1564, 1951. (*l*) Mackey, W. A., and Shaws, G. B.: Oral Hexamethonium Bromide in Essential Hypertension, Brit. M. J. **2**:259, 1951. (*m*) Shapiro, A. P., and Ferris, E. B.: The Effects of Intravenously Administered Veratrum Viride in Hypertension and Normotensive Subjects, Ann. Int. Med. **36**:792, 1952. (*n*) Anderson, W. B.: Fundus Changes Before and After the Rice Diet, Tr. Am. Acad. Ophth. **55**:627, 1951. (*o*) Rice, T. B.: Low-Sodium Diet: A Manual for the Patient, Philadelphia, Lea & Febiger, 1951. (*p*) Loofbourow, D. G.; Callahan, D., and Palmer, R. S.: A Rice Diet in Ambulatory Patients with Essential Hypertension: A Two-Year Study of 105 Patients, New England J. Med. **244**:577, 1951. (*q*) Wolferth, C. C.; Jeffers, W. A.; Lukens, F. D. W., and others: Observations on Results of Subtotal Adrenalectomy in Treatment of Severe, Otherwise Intractable Hypertension and Their Bearing on Mechanism by Which Hypertension is Maintained, Ann. Int. Med. **35**:8, 1951. (*r*) Borsook, H., and Borsook, M. E.: Biochemical Basis of Betaine-Glycocyamine Therapy, Ann. West. Med. & Surg. **5**:825, 1951. (*s*) Graybiel, A., and Patterson, C. A.: Use of Betaine-Glycocyamine in Treatment of Patients with Heart Disease, ibid. **5**:863, 1951. (*t*) Feinberg, A. W., and Rosenberg, B.: Use of Carboxylic Cation Exchange Resins in Therapy of Congestive Heart Failure, Am. Heart J. **42**:698, 1951. (*u*) Wood, J. E., Jr.;

(Footnote continued on next page)

pentamethonium bromide and hexamethonium bromide, may produce visual disturbances, such as partial cycloplegia and dilation of the pupil. In many patients a reduction in intraocular pressure follows their use.

The work of Graybiel and Patterson [209s] and of the Borsooks [209r] would demonstrate that larger-than-normal amounts of creatinine may be beneficial in conditions of muscular weakness or degeneration, including cardiac failure and some neurological conditions. The immediate precursor of creatinine in the animal is glycocyamine, or guanidoacetic acid. It is synthesized from arginine and amino acetic acid (glycine) in the kidney. Glycocyamine is then transported to the liver, where it is methylated by methionine to form creatinine; but there is experimental evidence that the betaine can supply the necessary methyl group. The daily dose by mouth is glycocyamine, 30 mg. per pound (0.5 kg.) of body weight, and betaine hydrate, four to five times

TABLE 4.—*Therapy of Essential Hypertension*

Therapy	Value
Sedatives	
Potassium bromide, chloral hydrate...	Helpful with tense, anxious and irritable patients
Propylthiouracil; I^{131}	Of aid with tense, irritable patients
Diet	
Calories	Total caloric intake to be reduced for overweight patient
Salt	Salt intake to be reduced, below 500 mg.
Cation exchange resins.....	Of aid in maintenance of low sodium intake
Rice diet	Low in salt, low in cholesterol, low in calories, low in nitrogen; value depends on efficacy of sodium restriction
Low cholesterol-low fat.....	Evidence not conclusive as to value of dietary limitation in this regard; however, may be considered as suggestively beneficial
Surgery	
Sympathectomy	Of value in patients showing objective evidence of progressive ocular disease, for those whose medical management has failed or is impractical
Total adrenalectomy	Requirements: close surveillance, regulation of adrenocortical therapy, adequate renal function
Drugs	
Potassium thiocyanate	Blood level of 3 to 6 mg./100 cc. desirable for control of headache
Blocking agents	Attempt to obtain medical sympathectomy
Autonomic-ganglion-blocking agents (*a*) Pentamethonium iodide (*b*) Hexamethonium iodide (*c*) Tetraethylammonium chloride	Undesirable side-effects, e. g., loss of accommodation, postural hypotension; short-term action
Adrenergic-blocking agents ..... e. g. Benzodioxane	Chief value in diagnosis
Veratrum alkaloids	Effective dose close to toxic one, helpful in a few patients
Sodium nitroprusside	Helpful in a few patients
l-Hydrazinophthalazine ..... ("apresoline")	Overcomes a vasopressor substance of central origin; helpful in some patients with malignant hypertension
"Pyrogen"	Of little help
Mixed therapy	Combinations of above methods, properly selected, helpful

the dose of glycocyamine. The two substances are usually taken together, the glycocyamine in tablets and the betaine dissolved in water, the total daily dose being divided into four or five portions, to be given through the day.

Ferguson, D. H., and Lawrence, T.: Cation Exchange Resins as an Adjunct in Treatment of Heart Failure, J. A. M. A. **148**:820, 1952. (*v*) McChesney, E. W.; Dock, W., and Tainter, M. L.: Ion Exchange Resins in Edema, Medicine **30**:183, 1951. (*w*) Nickel, J. F.; Lowrance, P., and Leifer, E.: Effect of Sodium Depletion and Repletion on Renal Function and Body Fluids During Uremia, J. Clin. Invest. **30**:664, 1951. (*x*) Martz, B. L.; Kohlstaedt, K. G., and Helner, O. M.: Use of a Combination of Anion and Cation Exchange Resins in the Treatment of Edema and Ascites, Circulation **5**:524, 1952. (*y*) Danowski, T. S.; Greenman, L.; Reters, J. H., and Mateer, F. M.: An Introduction to Experimental and Clinical Studies of Carboxylic Cation Exchange Resins, J. Clin. Invest. **30**:979, 1951. (*z*) Duncan, C. F.: Theory and Practice of Ion Exchange, Nature, London **169**:22, 1952.

Cation Exchange Resins.—Cation exchange resins are insoluble substances, natural or synthetic, which remove one ion from solution in exchange for another. Cation exchanges remove sodium, potassium, and calcium ions from solution. Most cation exchange resins in clinical use are synthetic. Restriction of sodium in the diet has been accepted as helpful in the management of many patients with congestive heart failure and certain patients with other forms of edema, but the ideal sodium intake cannot always be accomplished by diet alone. The cation exchange resin is not a cure-all, and not a complete solution to the sodium-restriction problem of patients with edema. The chief dangers are the low-salt syndrome, azotemia, and mild or moderate transient acidosis when one uses an ammonium-potassium cation resin. Impaired renal function is the outstanding contraindication to its use.[210]

Reaction of the Conjunctival Vessels in Hypertensive Patients to Topically Applied Epinephrine.—Lee and Holze [211s] studied the vessels of the bulbar conjunctiva by means of slit-lamp microscopy. An over-all pattern of certain peripheral vascular abnormalities in hypertension emerged. However, not one of them was characteristic of hypertension alone. The authors found metarteriolar narrowing, increased spontaneous vasomotor activity in precapillary sphincters, and coiling, looping, and tortuosity of many vessels. There were also a heightened sensitivity of metarterioles and precapillaries to topically applied epinephrine and a reduced velocity of peripheral blood flow. These features are generally in accord with those that have been described for similar vessels in the splanchnic area of animals with experimental renal hypertension.

MYASTHENIA GRAVIS

Therapy.—According to Schlezinger, [212] combined neostigmine and ephedrine medication remains the treatment of choice for most patients with myasthenia gravis. Potassium and guanidine show a relatively slight beneficial effect as compared with neostigmine, but undesirable side-effects limit their usefulness. Tetraethylpyrophosphate and octamethylpyrophosphoramide show a maximum therapeutic effect approximating that of neostigmine, but of longer duration. However, toxic reactions and difficulty of adjustment of the optimum dose make the routine use of these drugs impractical. A concurrence of hyperthyroidism and myasthenia gravis should be treated medically, primarily by elimination of hyperthyroidism through the use of propylthiouracil or radioactive iodine, which appear to influence myasthenia gravis favorably.

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210. Feinberg and Rosenberg.[209t] Wood and others.[209u] McChesney, Dock, and Tainter.[209v] Nickel, Lowrance, and Leifer.[209w] Martz, Kohlstaedt and Helner.[209x] Lippman, R. W.: Cation Exchange Resin in Treatment of Nephrotic Syndrome, A. M. A. Arch. Int. Med. **88**:9, 1951. Chapman, D. W.; Pannill, F. C., Jr., and Skaggs, R. H.: New Cation Exchange Resins in Therapy of Edematous States, Am. Pract. & Digest. Treat. **2**:945, 1951. Emerson, K., Jr.; Conn, S. S.; Vester, J. W., and Nelson, K. P.: Oral Use of Cation Exchange Resins in Treatment of Edema, A. M. A. Arch. Int. Med. **88**:605, 1951. McChesney, E. W.; Dock, W., and Tainter, M. L.: Ion Exchange Resins in Edema, Medecine **30**:183, 1951. Flanagan, T. L.; Sax, M. F., and Heming, A. E.: Toxicity Studies on Amberlite XE-96, A Carboxylic Type Cation Exchange Resin, J. Pharmacol. & Exper. Therap. **103**:215, 1951. McChesney, E. W.: Studies on Cation Exchange Resins, J. Lab. & Clin. Med. **38**:199, 1951.

211. Lee, R. E., and Holze, E. A.: Peripheral Vascular Hemodynamics in Bulbar Conjunctiva of Subjects with Hypertensive Vascular Disease, J. Clin. Invest. **30**:539, 1951.

212. Schlezinger, N. S.: Present Status of Therapy in Myasthenia Gravis, J. A. M. A. **148**:508, 1952.

Thymectomy should be reserved for patients with a demonstrable thymoma and a few selected patients whose disease appears to be inadequately controlled with neostigmine and who are not benefited by corticotropin therapy. When indicated, thymectomy offers better hope of permanent relief in myasthenia gravis than does neostigmine, particularly if carried out early.[213] Corticotropin therapy results in relapse during the course of treatment, with noteworthy partial remission within 72 hours following termination of therapy, subsequent relapse may occur, and the ultimate therapeutic benefit remains undetermined.

McKeever has reported the seventh known case of myasthenia occurring in a newborn child of a myasthenic mother.

The myasthenia of the newborn infant was not evident on the first day but became evident on the second day, and subsequently all symptoms of the disease disappeared by the 15th day. This course is the usual one. The transient nature of neonatal myasthenia has been observed previously.[214]

The cause of myasthenia gravis is not known. It has been postulated that it may be due to a deficiency in acetylcholine, that is, a deficiency in the formation of acetylcholine, or it may be due to an excess of cholinesterase, or perhaps it is due to some curare-like substance circulating in the tissues and blood stream. It is apparent that whatever the factor which is at fault, it is capable of passing through the placental barrier, and that it is not persistent, for the infant whose case is described improved spontaneously within two weeks. Thus, this clinical observation on a newborn infant with the condition, having been born of a mother with myasthenia gravis, suggests that there had been a transference of a curare-like substance across the placental barrier. There is also the possibility that there had been an excess of cholinesterase which has passed from the mother into the baby, or that the infant was responding to the neostigmine which was given the mother and had adjusted its system to utilization of the neostigmine which was being supplied through the mother. When the neostigmine was removed, the infant had a period of readjustment to go through. Thus, the excess amount of the anticholinesterase drug in the infant's system demanded that the infant produce more cholinesterase to carry on its normal body functions. When the neostigmine was removed from the infant by virtue of birth, excess cholinesterase was being formed for several weeks, until it no longer was necessary for the infant to use quite as much neostigmine; or the excess cholinesterase in the infant may have come from the mother, and gradually, as it was depleted in the infant, there was no longer any need for the neostigmine. It is interesting that no case of myasthenia gravis in infancy had been observed prior to the introduction of neostigmine, in 1935.

Electromyographic studies of the orbicularis oculi muscle by Botelho, Deaterly, and Comroe revealed that this muscle in patients with myasthenia gravis may be affected earlier or more severely than muscles of the extremities. This method may be helpful in diagnosis. The electromyogram of this muscle may be characteristic of neuromuscular block at a time when electromyographic studies of the hand are normal.[215]

Relation of Blood Lipids to Therapy.—There has been a recent revival of interest in the theory concerning the possibility of the relation of serum cholesterol levels to the development of atherosclerosis, both experimentally and clinically.[216] Two opposing views exist: One states that human atherosclerosis is caused by eating a diet rich in cholesterol, and that this form of vascular damage may be favorably influenced through the diet. It has been fairly well shown that it is very difficult to influence the serum cholesterol levels by diet unless one is especially

213. Schlezinger.[212] Holmes Sellors, T.: Surgery of the Thymus Gland and Myasthenia Gravis, Arch. Middlesex Hosp. **2**:1, 1952. Kemp Harper, R. H.: The Investigation of Thymic Tumors in Myasthenia Gravis, J. Fac. Radiologists **3**:164, 1952.

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215. Botelho, S.; Deaterly, C. F., and Comroe, J. H., Jr.: Electromyogram from Orbicularis Oculi in Normal Persons and in Patient with Myasthenia Gravis, A. M. A. Arch. Neurol. & Psychiat. **67**:348, 1952.

strict and uses an essentially fat-free, cholesterol-free, rice-free diet, which provides little sodium and is probably deficient in calories, and unless one combines this with thyroid substance.

There are many unsolved problems and conflicts concerned with this subject, and at present one cannot make a prognosis as to the atherosclerosis and as to its effects based on blood-lipid values alone. However, several tentative conclusions may be drawn. Total blood cholesterol is not a reliable indicator of vascular damage, and several new factors command attention, such as the cholesterol-phospholipid ratio, cholesterol in the β-globulin fraction, and the cholesterol of specific dimensions revealed by analytical ultracentrifugation.[216] There is evidence that lipotropic agents, such as choline and inositol, may be helpful in reduction of atherosclerosis clinically and experimentally. Inositol has been reported as reducing cholesterol levels of blood in diabetic patients but to be of negative value in the treatment of atherosclerosis in diabetes mellitus. Other investigators have found these lipotropic agents to be of no value in preventing or ameliorating experimentally induced atherosclerosis in laboratory animals.[216m-p] Study of the lipoproteins by ultracentrifugation has revealed that of the two classes of serum lipoproteins which are strongly associated with atherosclerosis, the Sf35-100 class is moderately related to obesity, whereas the Sf12-20 class shows a much slighter, yet significant, relationship to obesity. Lipoproteins of the class Sf12-100, representing only 10 to 15% of the serum cholesterol, are strongly associated with atherosclerosis. The positive correlation of atherosclerosis with the Sf12-100 class and that of obesity with the Sf35-100 class provide part of the basis for the belief in the relation of obesity to atheromatous vascular disease. This subtle relationship is almost

216. (*a*) Chaikoff, I. L., and Chernick, S. S.: Significance of Endogenous Cholesterol in Arteriosclerosis, Science **113**:47, 1951. (*b*) Blood Lipids in Atherosclerosis, editorial, J. A. M. A. **148**:207, 1952. (*c*) Keyes, A.: (Cholesterol Giant Molecules) in Atherosclerosis, ibid. **147**:1514, 1951. (*d*) McMahon, A.; Allen, H. N.; Weber, C. J., and Missey, W. C., Jr.: Hypercholesterolemia, South. M. J. **44**:993, 1950. (*e*) Stampler, J., and Katz, L. M.: Effect of Pancreatectomy on Lipemia, Tissue Lipidosis and Atherogenesis in Chicks, Circulation **4**:255, 1951. (*f*) Pollak, O. J., and Wadler, P.: Studies in Experimental Atherosclerosis, J. Gerontol. **6**:217, 1951. (*g*) Fredman, M.; Byers, S. O., and Rosenman, R. H.: Accumulation of Serum Cholate and Its Relationship to Hypercholesterinemia, Science **115**:313, 1952. (*h*) Wilmot, V. A., and Swank, R. L.: The Influence of Low-Fat Diet on Blood Lipid Levels in Health and in Multiple Sclerosis, Am. J. M. Sc. **223**:25, 1952. (*i*) Kellner, A.: Lipid Metabolism and Atherosclerosis, Bull. New York Acad. Med. **28**:11, 1952. (*j*) Priddle, W. W.: Hypercholesteremia, Ann. Int. Med. **35**:836, 1951. (*k*) Tuttle, E.: Dietary Cholesterol and Atherosclerosis, Geriatrics **7**:37, 1952. (*l*) Pollak, O. J.: Report on Current Trends in Arteriosclerosis Research, ibid. **7**:59, 1952. (*m*) Popkin, R. J.: Evaluation of Inositol in Treatment of Arteriosclerosis Obliterans, Angiology **2**:398, 1951. (*n*) Morrison, L. M.: Arteriosclerosis, J. A. M. A. **145**:1232, 1951. (*o*) Davidson, J. D.; Meyer, W., and Kendall, F. E.: Effect of Choline upon Experimental Canine Arteriosclerosis, Circulation **3**:332, 1951. (*p*) Gofman, J. W.; Lindgren, F. T.; Jones, H. B.; Lyon, T. P., and Strisower, B.: Lipoproteins and Atherosclerosis, J. Gerontol. **6**:105, 1951. (*q*) Gold, H.: Low Cholesterol Diet in the Treatment of Atherosclerosis, Am. J. Med. **12**:357, 1952. (*r*) Lindgren, F. T.; Elliott, H. H., and Gofman, J. W.: The Ultracentrifugal Characterization and Isolation of Human Blood Lipids and Lipoproteins with Applications to the Study of Atherosclerosis, J. Phys. & Colloid Chem. **55**:80, 1951. (*s*) Gofman, J. W., and Jones, H. B.: Obesity, Fat Metabolism and Cardiovascular Disease, Circulation **5**:514, 1952. (*t*) Pierce, F. I., Jr.: The Relationship of Serum Lipoproteins to Atherosclerosis in Cholesterol Fed Alloxanized Rabbit, ibid. **5**:401, 1952. (*u*) Steiner, A.; Kendall, F. E., and Mathers, J. A. L.: The Abnormal Serum Lipid Pattern in Patients with Coronary Arteriosclerosis, ibid. **5**:605, 1952. (*v*) Epstein, N. N.; Rosenman, R. H., and Gofman, J. W.: Serum Lipoproteins and Cholesterol Metabolism in Xanthelasma, A. M. A. Arch. Dermat. & Syph. **65**:70, 1952. (*w*) Van Itallie, B. T.; Waddell, W. R.; Geyer, R. P., and Stone, F. J.: Clinical Use of Fat Injected Intravenously, A. M. A. Arch. Int. Med. **89**:353, 1952. (*x*) Eggers, H.: Lipotropic Substances for the Absorption of Vitreous Opacities, New York. J. M. **51**:2255, 1951.

entirely obscured by the total serum cholesterol measurements. It would seem from these studies that the control of obesity might be of importance in the therapy of atherosclerosis.[217]

Xanthelasma is considered to be a common external manifestation of essential xanthomatosis (familial hypercholesteremia). It appears from the studies of Epstein and co-workers[216v] that what was formerly regarded as a cosmetic defect must, in the light of recent blood chemistry research, such as ultracentrifugation of the lipoproteins, be more than an occasional forerunner of conditions threatening longevity.

Van Itallie and his co-workers[216w] have demonstrated successfully the clinical use of fat emulsions by intravenous administration as a method of parenteral feeding.

Eggers is convinced that lipotropic substances facilitate the absorption of vitreous opacities in those cases in which they are not due to active focal or constitutional infection. The mode of action of these substances for clearing of vitreous opacities was not presented.[216x]

HISTAMINE AND ANTIHISTAMINICS

Histamine is a normal constituent of blood, the granular series of leucocytes being its main source. Part or all of the histamine originates with the cells of the blood in the bone marrow, but the means by which it enters these cells, or is synthesized, is not known. Histamine is released from the blood cells by trauma, by clotting, and by antigen-antibody reaction. The leucocytes vary in the amount of histamine contained.[218]

Cuco[219] has demonstrated that the permeability of the rabbit eye to the intraocular penetration of fluorescein was increased after the subcutaneous, intravenous, retrobulbar, or conjunctival instillation of histamine. D'Ermo[220] found traces of histamine in the aqueous humor of the rabbit eye at the height of an experimentally induced anaphylactic reaction.

A slight, but definite, depressant effect on the atopic skin reactions following the use of corticotropin has been reported by Bowman and his co-workers. They were unable, however, to influence the skin reactions induced by histamine with such therapy.[221]

Shure and Harris[222] have prepared an imposing list of the antihistaminic drugs. One is impressed with the great number of these drugs and with the increasing number of other drugs which have been added to the antihistaminics in an effort to produce greater effectiveness. The increase in numbers is understandable because of the desire on the part of the manufacturers to perfect a product with greater effectiveness and less undesirable side-reactions. The addition of independently effective drugs, however, seems a definite admission that the antihistaminics alone are lacking in effectiveness. Many mixtures contain acetylsalicylic acid, acetophenetidin, caffeine, and codeine. One even contains a vaccine of a bacterium common in infections of the upper respiratory tract. It is well to realize what one is using when one prescribes antihistaminic agents, and one should not lose sight of the primary physiologic action desired[222] (Table 5).

Many toxic reactions to antihistaminics have been reported. Azzolini and Faldi[223] have shown that the peritoneal introduction of some antihistaminic agents produced a sutural type of cataract in guinea-pig eyes.

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217. Editorial.[216b] Kellner.[216i] Tuttle.[216k] Pollak.[216l] Gofman and others.[216p] Gold.[216q] Lindgren, Elliott, and Gofman.[216r] Gofman and Jones.[216s] Pierce.[216t] Steiner, Kendall, and Mathers.[216u]

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TABLE 5.—*Commercially Available Antihistamine Compounds*

Antistine® (Antazolin hydrochloride) (Ciba Pharmaceutical Products, Inc.)	Tablets: 100 mg. Ophthalmic solution: 0.5%
Benadryl® (Diphenhydramine) (Parke, Davis & Company)	Capsules: 25 and 50 mg. Capsules: 50 mg. with ephedrine, 10 mg. Tablets: 50 mg., delayed-action coating Elixir: 10 mg./tsp. Sterile solution: for parenteral use, 10 mg./cc. Cream: 2% in water-miscible base
"Cehistra" * (Organon, Inc.)	Effervescent tablets of antihistaminic with acetylsalicylic acid and ascorbic acid
"Chlorothen" (Chloromethapyrilene citrate) (Whittier Laboratories)	Tablets: 25 mg. Caubren® Compound: Contains "chlorothen" 25 mg., acetophenetidin, and caffeine
"Chlor-trimeton" (Chlorprophenypyridamine maleate) (Schering Corporation)	Tablets: 4 mg. "Repeat Action Tablets": 8 mg., especially coated to produce immediate and delayed actions Syrup: 2 mg./tsp. Coricidin®: "Chlor-trimeton," 2 mg. with acetylsalicylic acid, acetophenetidin, and caffeine
Decapryn succinate® (Doxylamine succinate) (The Wm. S. Merrell Company)	Tablets: 12.5 and 25 mg. Syrup: 6 mg./tsp. Compound with sodium salicylate: Contains decapryn succinate®, 6 mg. with sodium salicylate and caffeine With Ape: Decapryn® with acetylsalicylic acid, acetophenetidin and caffeine "Minergic" solution: For penicillin diluent
Diatrin® hydrochloride (Methaphenile hydrochloride) (William R. Warner & Company, Inc.)	Tablets: 50 mg.
"Diparalene" (Chlorcyclizine hydrochloride) (Abbott Laboratories)	Tablets: 25 and 50 mg., claimed to be long-acting
Dramamine® (Dimenhydrinate) (G. D. Searle & Company)	Tablets: 50 mg. Liquid: 12.5 mg./tsp., advocated for relief of motion sickness
"Foralamin," J. Pharmacol. & Exper. Therap. Aug. 1950, p. 479 (Eaton)	Tablets: 50 mg.
Proketuss® (Sharp & Dohme, Inc.)	Syrup: Contains 10 mg. methapyrilene hydrochloride, 15 mg. propadrin®, 150 mg. potassium citrate, 15 mg. chloroform, 1 mg. menthol, 5% alcohol in each teaspoonful
Pyribenzamine® (Tripelennamine citrate) (Ciba Pharmaceutical Products, Inc.)	Tablets: both delayed and rapid-acting, 50 mg. Tablets: 25 mg. with 12 mg. ephedrine Elixir: 30 mg./tsp. Expectorant: Contains 30 mg. tripelennamine citrate, 10 mg. ephedrine, 80 mg. ammonium chloride /tsp. Nasal solution: 0.5%; also dispensed in a nebulizer Ointment: 2% in petrolatum Cream: 2% in water-miscible base
Pyrrolazote® (The Upjohn Company)	Tablets: 25 and 50 mg. Tablets: Delayed acting, 50 mg. Elixir: 10 mg./tsp. "Pyrroxate": Contains pyrrolazote,® orthozine, acetylsalicylic acid, acetophenetidin, and caffeine; also available with codeine phosphate, gr. ¼ (15 mg.)
Tagathen® (Chloromethapyrilene) (Lederle Laboratories)	Tablets: 25 mg.
Thenfadil® (Winthrop-Stearns, Inc.)	Tablets: 15 mg. Neosynephrinethenfadil®: 0.25% phenylephrine and 0.1% thenfadil®
Thenylene® hydrochloride (Methapyrilene hydrochloride) (Abbott Laboratories)	Tablets: 25, 50 and 100 mg. Thenylene with desoxyn®: 50 mg. thenylene® and 2.5 mg. metamphetamine "Thenylene® APC": 25 mg. metapyrilene plus acetylsalicylic acid, acetophenetidin, and caffeine "Thenylfred": Thenylene® plus ephedrine; also available with "glucophylline" Cream: 2% in water-miscible base
Thephorin® (Phenindamine) (Hoffmann-LaRoche, Inc.)	Tablets: 25 mg. Syrup: 10 mg./tsp. Ointment: 5% in "carbowax" base "Thephorin®-AC": Thephorin® plus acetylsalicylic acid, acetophenetidin, and caffeine Expectorant: Thephorin® plus codeine, papaverine, ammonium chloride, and chloroform Lotion: 2 and 5%
"Topaminic" (Metapyrilene) (Sharp & Dohme, Inc.)	Cream: 2% antihistaminic, 8% calamine, 3% benzocaine and 0.05% hexylated cresol
"Tri-histon" (Recsei)	Tablets: 25 and 50 mg. (a mixture of three antihistaminics)
Trimeton® (Schering Corporation)	Tablets: 25 and 50 mg. Elixir: 7.5 mg./tsp. Cream: 3% in water-miscible base Lotion: 2% in modified calamine lotion Solution: 0.5% "Trimetose": Cough syrup containing trimeton,® ammonium chloride, sodium citrate, chloroform, and menthol

There are several antihistaminic compounds advertised and sold as patent medicines without a doctor's prescription. Among these are:

Kripton (4)
Resistab (7)
Antamine (4)
"Inhiston" (2)
Anabist (7)
Tabcin (Metapyrilene)

* Trimeton,® ascorbic acid, and salicylic acid is an alkalizing base.

One of the main undesirable effects of the antihistaminics in therapeutic dosage appears to be due to depression of higher centers. The symptoms observed from overdosage often appear to result from stimulation of the central nervous system. Children appear to be particularly susceptible to the convulsive action of the antihistaminics.[224] Barbiturates antagonize the stimulating effects of some antihistaminics on the central nervous system.[224a]

Guerrant and Hollifield[225] report three cases in which severe palpebral dermatitis followed the use of antihistaminics in ophthalmic solution. In one case the symptoms developed within a month after initial onset of use of the drug, and in the others therapy was carried on over a year before the allergy appeared.

Komi[226] concludes from his studies that the antihistaminic drugs increase sympathetic, or adrenergic, stimuli to the eye. When antihistaminic drugs were injected intravenously, the intraocular pressure, as well as the blood pressure rose, but the aqueous still showed little antihistaminic activity.[226] Most of the antihitaminics tested by Komi were shown to have some mydriatic effect, which was not proportional to the concentration of the drug in the aqueous humor. Subconjunctival injections which liberate no histamine increase the potency of these agents in the anterior chamber. Antihistaminics produce a mydriatic effect which could overcome the miotic effect of pilocarpine, and these drugs seemed to promote the mydriatic action of epinephrine to produce maximal dilation of the pupil. D'Ermo and his associates[227] have demonstrated for antihistaminic solutions antibacterial activity, local anesthetic properties, which were slightly greater than that of a 1% cocaine solution, and a tension-lowering effect. These investigators found that some antihistaminics, such as 1% dimetine, (dimethylaminoethylbenzylamine), produced constriction of the pupil, whereas most of the others produced dilation. When these agents were used in concentrations for local anesthetic properties, they produced damage to the corneal epithelium. None of the antihistaminics tried seemed to influence accommodation.

D'Ermo also points out that these agents are helpful in a variety of allergic ocular conditions.[228]

Antihistaminics apparently had no effect on the pain threshold.[229]

When carbachol U. S. P. or other choline esters are injected beneath the skin, it has an urticarogenic action. This can be modified or obliterated by an antihistaminic drug. Thus, according to these authors, antihistaminics would appear to have an antiacetylcholine action. However, other investigators believe that this is not so, as the effect is too weak, and they believe that the predominant effect must be exerted by or through histamine. In other words, with an antidromic impulse there is release of acetylcholine. This causes release of acetylcholine at the nerve ending; this, in turn, causes release of histamine, which actually is responsible for the vasodilation. According to these authors, it is this histamine which is blocked by the antihistaminic agent and thus reduces the urticarogenic action of the choline esters.[230]

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TOXICOLOGY [231]

There are many drugs that can produce a variety of blood disorders.[231a]

Neutropenia and Agranulocytosis

Sulfonamides
Thiourea and derivatives
Aminopyrine (pyramidon®)
Organic arsenicals
Gold salts
Antihistaminics (tripelenamine [(pyribenzamine®])
Diethazine and hydrochloride "diparcol"
Tridione® (trimethadione)
Mesantoin®
X-rays
Radium
Radioactive isotopes

Thrombocytopenia and Purpura

Sedormid® (allylisopropylacetyl carbamide)
Organic arsenicals
Sulfonamides
Gold salts
X-rays
Radium
Radioactive isotopes

Aplastic Anemias

Drugs producing thrombocytopenia and purpura
Folic-acid antagonists
Nitrogen mustard
Quinacrine (atebrine®)
Bismuth
Colchicine
Chloroamphenicol (chloromycetin®)
X-rays
Radium
Radioactive isotopes

Hemolytic Anemias

Phenothiazine (thiodiphenylamine)
Phenylhydrazine
Antihistaminics and quinine
Sulfones and mephenesin (myanesin®)

Blood Pigment Disorders, Such as Enterogenous Cyanosis [231b]

Sulfonamides
Pyridium (phenyazo-a, a-diaminopyridine monohydrochloride)
Acetophenetidin (phenacetin)
Sulphonal (sulfonmethane)
Potassium chlorate
Acetanilid

Modell and Patterson have reported intestinal bleeding associated with acetylsalicylic-acid therapy.[231c]

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231. (*a*) Chalmers, J. N. M.: Drug-Induced Blood Disease, Practitioner **168**:235, 1952. (*b*) Menzel, W., and Wilhoeft, I.: Hyperplastic Late Reaction of Blood-Forming Organs to Intoxication with Dichlor-Diethyl Sulfide (Mustard Gas), Folia hæmat. **70**:278, 1951. (*c*) Modell, W., and Patterson, R.: Intestinal Bleeding Associated with Acetylsalicylic Acid, J. A. M. A. **147**:124, 1951. (*d*) Gelfand, M. L.: Visual Symptoms After Digitoxin Therapy, ibid. **147**:1231, 1951. (*e*) Cohen, B.: Digitalis Poisoning and Its Treatment, New England J. Med. **246**:254; 225, 1952. (*f*) Brooke, C., and Boggs, T.: Boric Acid Poisoning, A. M. A. Am. J. Dis. Child. **82**:465, 1951. (*g*) Slinger, W. N., and Hubbard, D. M.: Treatment of Seborrheic Dermatitis with a Shampoo Containing Selenium Sulfide, A. M. A. Arch. Dermat. & Syph. **64**:41, 1951. (*h*) Filatova, B. C.: Toxicity of Selenium Anhydride, Gigiena Sanit. **5**:18, 1951. (*i*) Ahlborg, G.: Hydrogen Sulfide Poisoning in Shale Oil Industry, A. M. A. Arch. Indust. Hyg. **3**:247, 1951. (*j*) Davidson, H. H.; Hingson, R. A., and Hellman, L. M.: Use of Various Plastic Catheters in the Subarachnoid and Peridural Spaces, A. M. A. Arch. Surg. **62**:540, 1951. (*k*) Ridley, H.: Intra-Ocular Acrylic Lenses: Recent Development in Surgery of the Cataract, Brit. J. Ophth. **36**:113, 1952; (*l*) Tr. Ophth. Soc. U. Kingdom **71**:617, 1951; (*m*) Intra-Ocular Acrylic Lenses After Cataract Extraction, Lancet **1**:118, 1951. (*n*) Vail, D.: Lint in the Anterior Chamber Following Intraocular Surgery, Am. J. Ophth. **34**:1533, 1951. (*o*) Enns, J. H.: Human Galactosemia Cataract, ibid. **34**:1268, 1951. (*p*) Reiter, C., and Lasky, M. A.: Galactose Cataractogenesis, ibid. **35**:69, 1952. (*q*) Falls, H. F.; Lowrey, G. H.; Anderson, W., and Glayton, C., Jr.: Galactosemia Cataract, ibid. **34**:1271, 1951. (*r*) Bellows, J.: Lens and Vitreous, A. M. A. Arch. Ophth. **47**:516, 1952. (*s*) Daily, L., Jr.; Zeller, E. A.; Wakin, J. G.; Herrick, J. F., and Benedict, W. L.: Microwaves and the Lens, Am. J. Ophth. **34**:1301, 1951. (*t*) Morillas, D.: Spastic Paraparesis and Bilateral Cataract Following an Electric Shock, Actas luso-españ. neurol. y psiquiat. **10**:69, 1951. (*u*) Habenberger: Change in the Fundus After a Lesion Due to a High-Frequency Current, Wien. klin. Wchnschr. **63**:209, 1951. (*v*) Lijo Pavia, J.: Radiations and the Ocular Alterations They Produce, Rev. oto-neuro-oftal. **26**:25, 1951. (*w*) Sykowski, P.: Ethylene Glycol Toxicity, Am.

(Footnote continued on next page)

Toxic symptoms encountered with digitalis have been reported. They usually consist of blurring of vision, white and yellow vision, scotomas, seeing bright flickering lights, and seeing objects covered with snow outdoors only. The visual complaints, as reported by Gelfand,[231d] usually developed early in the course of digitoxin therapy and from the 4th to the 12th day. Cessation of administration of the drug for several days cleared the ocular disturbance, and the reintroduction of a smaller maintenance dose produced no ill-effects on vision.[231e]

Boric acid is used frequently, and only relatively few deaths have been reported in the literature. Quantities are lethal only when the drug is ingested accidentally and administered parenterally or when it is applied to a previously injured or diseased skin surface. The therapeutic value of boric acid is doubtful and its antiseptic quality minimal. There are better and safer substances available for use as antiseptics, irrigating solutions, wet dressings, and ointments. For this reason, boric acid or boric-acid solution should not be stocked on any of the floors, nurseries, or treatment rooms of hospitals, to be used indiscriminately.[231f]

Selsun® suspension, containing 2.5% selenium sulfide, together with a detergent, has been used with considerable success in seborrheic dermatitis of the scalp.[231g] Selenium anhydride, on the other hand, which is used in the manufacture of certain electrical appliances, has a pronounced effect upon the respiratory tract and the nervous system. When subjected to concentrations of 0.15 to 0.6 mg. per liter, or to 5 to 17.5 mg. per kilogram of body weight, rats showed conjunctival irritation and respiratory distress. The pupils dilated; convulsions set in, and the rats died in one to four hours. With chronic intoxication from exposure to this drug, conjunctival irritation was rather frequent.[231h]

After the loss of consciousness from an overdose of hydrogen sulfide, one sees nystagmus, as well as a Romberg sign. In subacute poisoning, one may see keratoconjunctivitis and irritation of other mucous membranes. No permanent damage to the eyes has been reported. This material is used in certain branches of the shale-oil-production industry.[231i]

Reaction of the Eye to Intraocular Plastics.—In experiments with various types of plastic catheters as anesthesia conduits in the caudal, peridural, and subarachnoid spaces of the central nervous system, Davidson and his co-workers found that radiopaque and nonradiopaque nylon ureteral catheters, and polyethylene and polyvinyl chloride catheters produced no reaction in the anterior chamber of the rabbit eye.[231j] Ridley's[231k-m] stimulating experience with intraocular acrylic lenses also demonstrates the ability of the intraocular structures to tolerate plastic substances.

Vail, on the other hand, stresses the importance of taking every precaution to prevent the introduction into the eye, during intraocular surgery, of cilia, of cotton or talc, or of oil droplets and ointments, for these produce undesirable reactions.[231n]

Cataract Produced by Toxins.—Galactose has frequently been reported as producing cataract in experimental animals. Only rarely has it been reported in man. Two cases of cataract formation associated with galactosemia have been reported during the past year.

J. Ophth. **34**:1599, 1951. (*x*) di Ferdinando, R.: Lead Poisoning with Optic Neuritis Due to the Morocco Leather of the Patient's Hat, Gior. ital. oftal. **4**:344, 1951. (*y*) Roda, E.: Iritis of Unknown Cause Treated with Nitrogen Mustard, Arch. Soc. oftal. hispano-Am. **11**:645, 1951. (*z*) Jimenez Diaz, C.: Treatment of Dysreaction Diseases with Nitrogen Mustards, Ann. Rheumat. Dis. **10**:144, 1951. (*a'*) Mitchell, R. G.: Laburnum Poisoning in Children, Lancet **2**:57, 1951. (*b'*) Fink, A. I.: Carbon Monoxide Asphyxia with Visual Sequelae, Am. J. Ophth. **34**:1024, 1951. (*c'*) Krejek, F.; Marlo, Z., and Soucek, B.: Experimental Carbon Disulfide Poisoning, Praktyka Lekanska, 1951, p. 124. (*d'*) Esente, I.: Ocular Manifestations in Acute Barbiturate Poisoning, Gior. ital. oftal. **4**:162, 1951. (*e'*) Pagliarani, N.: Neuro-ocular Complications Due to Antirabic Vaccination, Riv. oto-neuro-oftal. **26**:200, 1951. (*f'*) Sarkies, J. W. R.: Ophthalmoplegia Following a Scorpion Bite, Brit. J. Ophth. **35**:502, 1951. (*g'*) Roberts, A. E.: Platinosis: Five-Year Study of Effects of Soluble Platinum Salts on Employees in Platinum Laboratory and Refinery, A. M. A. Arch. Indust. Hyg. **4**:549, 1951.

Galactosemia is a hereditary congenital anomaly of carbohydrate metabolism in which the liver is apparently unable to convert galactose to glucose, permitting the accumulation of this substance in the blood, where it may exert a toxic effect on susceptible tissues, such as the lens. The diagnosis is made by findings of galactosuria and impaired galactose tolerance.[230o-r]

Cataract due to forms of radiation has been discussed in an earlier section, as well as cataract due to antihistaminics and ultrasonic radiation.

Electric shock has been reported as producing cataract, and high-frequency current, as producing a large central scotoma. The scotoma is probably due to spasm of the macular vessels, with subsequent macular edema.[230t-v]

Iridocyclitis Produced by Toxic Agents.—Iridocyclitis has been reported as being due to ethylene glycol instilled into the eye,[231w] and to lead poisoning from the Morocco leather of the patient's hat [231x] which had been colored with lead compounds. Associated with the iridocyclitis was a dermatitis of the forehead. It is interesting that iritis, which can be produced by locally instilled nitrogen mustard, has been reported as being benefited by the use of nitrogen mustard systemically.[231y]

Effects of Other Toxic Agents on the Eye.—Laburnum is a poisonous alkaloid and is present in all parts of the laburnum tree. The active principle stimulates and then paralyzes autonomic ganglia and has a central emetic action. One of the signs of such poisoning is mydriasis.[231a']

The cerebral effects following carbon-monoxide asphyxia are extremely varied. Severe reduction of visual acuity following exposure to gas is thought to be due to cortical blindness. Changes in the visual field do not conform to any single pattern.[231b'] Carbon disulfide has been shown again to have the ability to concentrate in the peripheral nervous system.[231c'] Barbiturate poisoning will also produce visual disturbances.[231d']

Rabies inoculation may produce optic neuritis, paralysis of extraocular muscles, and optic atrophy. Retinal hemorrhages have also occurred after such inoculations.[231e']

It is known that cobra venom has a neurotoxic element, which may be responsible for ophthalmoplegia. It has also been shown that there is a close similarity between the venom of the cobra and that of the scorpion. Sarkies [231f'] describes a case of peripheral neuritis of the third cranial nerve due to scorpion venom.

In addition to skin manifestations, definite inflammatory signs are produced in the conjunctiva and mucous membranes of the upper respiratory tract by platinum intoxication.[231g']

During the past four years there has been an increasing awareness of the toxicity of ferrous sulfate. Along with vomiting, loose stools, weak pulse, and semicoma, one sees dilated pupils. The treatment consists of transfusions of plasma or whole blood.[232]

Several new insecticides, such as dimethyl and diethyl *p*-phenylthiophosphate (parathion), are potent parasympathomimetic agents. Others of this group have been discussed in the section dealing with autonomic agents.[233]

Tetryl, tetralite, and pyrenite are industrial names for 2,4,6-trinitrophenylmethylnitramine. It is employed in the manufacture of explosives and is important as a booster charge. Typical tetryl dermatitis consists of itching of and around the eyes, followed by erythema and edema, papules, and then exfoliation of the skin of the eyelids. This dermatitis then extends to other parts of the face. Similar types of dermatitis have been reported associated with the manufacturing of plastics,[234] and contact dermatitis about the eyes in association with bamboo [235] has been reported.

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232. Duffy, T. L., and Drehl, A. M.: Ferrous Sulfate Poisoning, J. Pediat. **40**:1, 1952.

233. Deichmann, W. B.; Pugliese, W., and Cassidy, J.: Effects of Dimethyl and Diethyl Paranitrophenyl Thiophosphate on Experimental Animals, A. M. A. Arch. Indust. Hyg. **5**:44, 1952. Hamblin, D. O., and Marchand, J. F.: Parathion Poisoning, Am. Pract. & Digest Treat. **2**:1, 1951. Bidstrup, P. L., and Payne, D. J. H.: Poisoning by Dinitro-Ortho-Cresol, Brit. M. J. **2**:16, 1951. Aldridge, W. N., and Barnes, J. M.: Some Problems in Assessing Toxicity of the Organo-Phosphorus Insecticides Toward Mammals, Nature, London **169**:345, 1952.

234. Bergman, B. B.: Tetryl Toxicity, A. M. A. Arch. Indust. Hyg. **5**:10, 1952. Morris, G. E.: Condensation Plastics, ibid. **5**:37, 1952.

235. Schiff, B. L.: Contact Dermatitis Caused by Bamboo, A. M. A. Arch. Dermat. & Syph. **64**:66, 1951.

Beryllium Poisoning.—Acute and chronic disease of the skin, lungs, and entire body may result from exposure to beryllium, a metal recently adopted, but already in wide industrial use. Although no antidote has been found, corticotropin and cortisone frequently relieve symptoms and reverse granulomatous conditions. Some beneficial effect can be obtained by use of aurin tricarboxylic acid.[236] The condition can be diagnosed from a history of known exposure, symptoms, laboratory and roentgenologic data, and the finding of the metal in the urine, lymph nodes or other tissues. Beryllium inhibits alkaline phosphatase enzyme and displaces magnesium in other enzymes, causing widespread cellular disorders.

Silicon granulomas of the skin ordinarily do not undergo spontaneous involution. Improvement occurred coincident with aureomycin and therapeutic formula vitamin therapy. This would indicate that the improvement was not attributable to spontaneous improvement and that it may be explained on the basis of the effect of these medications on an associated undetermined infection. The microscopic changes seen in silicon granulomas of the skin resemble those described for beryllium, for talc and for asbestos.[237]

Leucotaxin when injected into the corneal parenchyma has been shown to produce inflammation within 24 hours. Histamines injected in a similar fashion produce mild transitory edema. These studies suggest that histamine is only a vascular poison, whereas leucotaxin is an inflammatory one.[238]

Treatment of Burns.—Many references appeared in last year's literature to the local and systemic therapy of burns. All articles stress that burns should be treated as emergencies, that the extent of the burn should be accurately recorded on the initial examination, that débridement of severe and extensive burns should be condemned, and that shock should be anticipated in severe cases. The use of blood transfusions and the necessity of restoring electrolyte balance have been stressed. Nutrition should be maintained, but not forced, and of course infection should be prevented. Most authors feel that grafting should be done as early as possible.[239] One of the new methods suggested for the treatment of burns consists in the application to the burned area of a partially hydrolyzed casein gel. The area is then covered with gauze impregnated with zinc acetate. The gel sets, forming a semipermeable membrane, which prevents the superficial loss of protein by the support given the damaged capillary bed and diminishes the protein loss into the burned area, thus minimizing local cellular damage and shock. With this method there are reported relief of pain, a minimum of infection, and definite splinting of the injured part.[240] Sulfhydryl compounds have received considerable attention for their value in the therapy of chemical corneal burns and injuries. They have variously been reported as beneficial by Cruithirds[241]; McLaughlin[242] and Harley,[243] however, stated that hydrosulphosol did not produce any significant beneficial effect either in the speed of healing or in the reduction of the incidence of secondary infection.

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236. Van Ordstrand, H. S.: Beryllium Poisoning, Ann. Int. Med. **35**:1203, 1951. White, M. R.; Finkel, A. J., and Schubert, J.: Protection Against Experimental Beryllium Poisoning of Aurin Tricarboxylic Acid, J. Pharmacol. & Exper. Therap. **102**:88, 1951. Sterner, J. H., and Eisenbud, M.: Epidemiology of Beryllium Intoxication, A. M. A. Arch. Indust. Hyg. **4**:123, 1951. Curtis, G. H.: Cutaneous Hypersensitivity Due to Beryllium, A. M. A. Arch. Dermat. & Syph. **64**:470, 1951.

237. Ginsberg, J. E., and Becker, L. A.: Silicon Granuloma of Skin Due to Traumatic Sand Inoculation, J. A. M. A. **147**:751, 1951.

238. Capri, A., and Alagna, G.: Action of Leucotaxin on the Cornea, Arch. ottal. **55**:7, 1951.

239. Leepton, C. H.: Treatment of Burns, J. Internat. Coll. Surgeons **17**:354, 1952.

240. Curtis, R. M.; Brewer, J. H., and Rose, I. W., Jr.: New Technique for Local Treatment of Burns, J. A. M. A. **147**:741, 1951.

241. Cruithirds, A. E.: Sulfhydryl Therapy in Ophthalmology: Progress Report, Ann. West. Med. & Surg. **5**:554, 1951.

242. McLaughlin, R. S.: Chemical Burns of the Eye, South. M. J. **44**:446, 1951; Hydrosulphosol as a Treatment of Chemical Burns of the Eye, Am. J. Ophth. **35**:21, 1952.

243. Harley, R. D.: An Experimental Study on the Evaluation of Hydrosulphosol in the Treatment of Ocular Injuries Due to Chemical Burns, Tr. Am. Ophth. Soc. **49**:557, 1951.

Again dimercaprol therapy has been shown to be of value in gold intoxication.[244] By combining with the gold, dimercaprol prevents the gold from interfering with sulfhydryl-containing enzyme systems.

Dimercaprol has been employed therapeutically in hepatolenticular degeneration (Wilson's disease) in an attempt to reduce the copper content of the brain and liver and thus possibly prevent further damage to these tissues. The Kayser-Fleischer ring has become fainter in a few cases after such therapy.[245]

Drug Fatalities.[246]—There have been 107 drug fatalities reported in the literature since December, 1946. These deaths were not from poisonings of the accidental or suicidal type, but occurred in the use of regularly advised and prescribed drugs. Of the drugs administered orally, bishydroxycoumarin (dicumarol®) was the commonest offender. Eleven fatal hemorrhages following its use have been reported since 1946. Fatalities from antiepileptic drugs, such as "mesantoin," trimethadione (tridione®), and phenacemide, and from sulfonamides continue to occur. Thiouracil has been responsible for two fatalities, and acetylsalicylic acid is reported as the cause of death in an infant and in an adult. Thiocyanates and ertron,® a vitamin-D preparation, have also been fatal.

Of the drugs given parenterally, antibiotics have been reported to have been the cause of 11 fatalities—penicillin of 6, and streptomycin of 5. Deaths from penicillin were due to exfoliative dermatitis, the Herxheimer reaction in syphilitic patients, and anaphylaxis. Streptomycin caused fatal toxic encephalopathy and dermatitis with stomatitis. Nine deaths from curare, due to respiratory arrest, have been reported. Mercurial diuretics, neoarsphenamine, aminophylline, tetraethylammonium chloride, hydrolysate (amigen®), protein producing anaphylactic shock, have been responsible for deaths. Certain diagnostic procedures, namely angiocardiography, cholecystography, and pyelography, have reportedly resulted in fatalities, and a sudden death due to anaphylactic reaction to an intradermal test has been reported in a woman aged 25, who had asthma and hay fever. It is important to note that a fatality following the use of neostigmine as a diagnostic test for myasthenia gravis has been recorded.[246a]

Physicians today have remarkable drugs with which to practice medicine, but, as is true of all tools, improper use is attended with danger. If unusual risk is associated with the use of a drug, but the physician is convinced that the drug is necessary in a particular case, or at least best suited to it, he should accept the risk as a challenge by which he cautiously approaches his clinical problem. To indict a drug or all drug therapy because occasional reactions are seen is unfair to patients who might benefit therefrom. However, the physician can ill afford, for his patient's welfare or his own reputation, to use a drug with which he is not familiar or which he believes too dangerous for his practice. It is true that occasionally, although a drug has been thoroughly studied, an unexpected reaction will occur. No one would deny the use of sulfonamides or antibiotics because they can cause worrisome reactions. Their value has been too well demonstrated to warrant their discard because of clinical disturbances in some patients. Physicians are well aware that drugs can do far more harm by misuse than by the occasional use of a drug which carries with it some risk. With adequate precautions and safeguards, the use of most drugs is not a dangerous procedure.[246b]

Atomic-Bomb Injury.[247]—The syndrome of acute radiation injury is a term applied to the symptom complex which results from exposure of the whole body, or major portion of it, to the initial nuclear radiation from an atomic bomb. This term should be clearly distinguished from irradiation sickness, which is commonly used to describe the symptom complex resulting

244. Strauss, J. S., and Rosenberg, E. J.: BAL Therapy of Gold Intoxication, Proc. Inst. Med. Chicago **18**:330, 1951.

245. Denny-Brown, D., and Porter, H.: Effect of BAL on Hepatolenticular Degeneration, Tr. Am. Neurol. A., 1951. Cummings, J. N.: Effects of BAL in Hepatolenticular Degeneration, Brain **74**:10, 1951.

246. (*a*) Flaxman, N.: Drug Fatalities, J. A. M. A. **147**:337, 1951. (*b*) The Use of New Drugs, editorial, ibid. **147**:62, 1951.

247. Dunham, C. L.; Cronkite, E. P.; Leroy, G. V., and Warren, S.: Atomic Bomb Injury: Radiation, Council on National Emergency Medical Service, ibid. **147**:50, 1951. Cady, L. D., and Miller, J. E.: A Symposium on Effects of Atomic Explosions, Mil. Surgeon **110**:165, 1952.

from therapeutic irradiation. It should also be distinguished from surface radiation injury. The latter term is properly applied to injuries of the skin and subcutaneous tissues resulting from x-radiation or from contact or near-contact with radioactive material. Internal radiation injury may result from the selective deposition, as in bone or thyroid, of radioactive material that has been inhaled or absorbed through the gastrointestinal tract or wound. The last two types of radiation injury may be caused by residual radioactive contamination. Initial nuclear radiation from the atomic bomb consists of gamma rays and neutrons admitted during the first minute after an atomic explosion. At the end of one minute 98% of the initial nuclear radiation has been delivered. The syndrome of radiation injury due to exposure of the whole body may occur as the result of any sort of atomic explosion—air bursts, surface bursts, or underwater bursts. The syndrome of acute radiation injury due to exposure of the whole body to the initial nuclear radiation of an atomic bomb occurs in three distinct forms—very severe, severe, and mild or moderate. The very severe forms are due to exposures of 600 r or more; the severe forms, to exposures of about 400 r, and the mild forms, to exposures of 200 to 300 r.

The diagnosis of the syndrome of radiation injury depends on the proper evaluation of three factors: 1. The probability that nuclear irradiation is sufficient to cause injury to reach the patient. 2. The existence of the development of any or all of the typical symptoms of radiation injury, such as the diagnostic sign of vomiting on the day of bombing. The early appearance of symptoms is indicative of greater severity of radiation injury. 3. The time trend of the appearance of leucopenia and lymphopenia. This should aid materially in the accurate evaluation of the severity of the injury. Dusky inflammation of the mucous membranes, soreness of the gums, and ulceronecrotic breakdown of tissue rarely occur before the third week. Hemorrhagic manifestations, other than cutaneous purpura, include epistaxis, menorrhagia, metrorrhagia, hemoptysis, and hematuria. Therapy should be directed to a restoration of water and electrolyte balance and the maintenance of general nutrition, control of infection, and treatment for hemorrhage and anemia.

The mechanical injuries suffered by virtue of atomic-bomb injury are no different from those incurred in warfare or in civilian accidents except that many will be complicated by burns and some of the effects of ionizing radiation. Ocular injuries are commonly associated with wounds of the head. Initial treatment should be conservative. It is best to evacuate patients with head injuries directly, and as expeditiously as possible, to areas where specialized medical knowledge is available.

Anoxia, a Possible Cause of Retrolental Fibroplasia.—The difficulties of pinning down the etiologic factors of retrolental fibroplasia are known to all ophthalmologists. Considerable interest has been shown recently in the suggestion that the improper administration of oxygen to the premature baby may be a responsible factor.[248] Szewzzky [248a] believes that he can induce retrolental fibroplasia in premature infants by removing them from oxygenated incubators and placing them in bassinets. He was able rapidly to reverse the changes of dilatation of vessels, hemorrhage, neovascularization, and retinal separation by placing infants back in an atmosphere of 60% oxygen concentration. In the bassinet the oxygen concentration was approximately 22%, and in incubators, about 50%. It is believed that retrolental fibroplasia is due simply to subclinical anoxia during a period when the incompletely developed retina utilizes oxygen at a rapid rate. The vascular engorgement in this disease is a compensatory mechanism. If the need for oxygen by the retina is met partially or completely by the dilated vascular channels, the disease develops either in its attenuated form or not at all.

Szewzzky,[248b] in a second report, states that premature infants should be given minimal amounts of oxygen, just sufficient to meet their needs, and weaned off slowly. Excessive oxygen concentration should be avoided. This assertion is confirmed in part by the experimental studies of Ingalls and his co-workers,[248c] who produced congenital malformations in the eye by develop-

248. (*a*) Szewzzky, S. T.: Retrolental Fibroplasia: Etiology and Prophylaxis, Am. J. Ophth. **34**:1649, 1951; (*b*) Retrolental fibroplasia, ibid. **35**:301, 1952. (*c*) Ingalls, T. H.; Tedeschi, C. G., and Helpern, M. M.: Malformations Induced by Maternal Anoxia, ibid. **35**:311, 1952. (*d*) Ryan, H.: Retrolental Fibroplasia, ibid. **35**:329, 1952. (*e*) Campbell, K.: Intensive Oxygen Therapy as a Possible Cause of Retrolental Fibroplasia, M. J. Australia **2**:48, 1951. (*f*) Lelong, N.; Renard, G.; Rossier, A.; Lemasson, C., and Michelin, J.: The Retinopathy of Premature Infants, Presse. méd. **59**:705, 1951.

ment of maternal anoxia. Ryan [248d] points out in his survey of the cases in Australia that no case occurred at one hospital prior to the introduction of a most efficient oxygen cot. With this apparatus, it was the practice of the nursing staff to give oxygen liberally to all babies, even when the infants apparently did not require it. Since October, 1950, oxygen has been given only to babies who were actually cyanosed; and since that date no further case of retrolental fibroplasia has occurred, although there have been many very premature and very small babies.

Campbell [248e] and Lelong and associates [248f] suggest that the normal oxygen environment of the newborn, full-term infant is abnormal for the premature infant, and that this is particularly so for infants of 32 weeks' gestation or less. The potential toxic effect of oxygen on premature infants can be enhanced by the administration of high concentrations of oxygen therapeutically, by fever, or by toxemia. The general vascular damage and edema so produced affect the eye and are starting points of retrolental fibroplasia. Campbell suggests that one carry the fetus to 33 weeks' gestation or more and then avoid intensive oxygen therapy. Oxygen should be given only when the infant is cyanosed, and not as a prophylactic measure. Only sufficient oxygen should be used to keep the infant's color satisfactory. In case the cyanosis is due to congenital cardiac defect, one should not make efforts to improve the infant's color with excess quantities of oxygen. Overheating should be avoided, and infection prevented; should the latter occur, treatment should be prompt and efficient.

Retinal Degeneration.—It has been shown by Lodato [249] that certain changes occur in the retinal tissues after the injection of sodium iodate and with subconjunctival grafts of pigmented tissues. According to Lodato, these changes are comparable to retinitis pigmentosa without pigment. He was able to reduce the changes produced by iodate by means of implants with retinal or uveal tissue.

Permeability of Membranes.—Harrell and Aikawa [250] show that the permeability of membranes is altered during the course of acute infections. This, in the early course of the disease, is probably induced by the toxemic products of the infective organisms. Later in the course of the illness, the defect may result from an immune reaction. In rickettsial diseases, for instance, the greatest alteration in permeability appears to come at a time when immunity is rising more rapidly. The point at which immunity overcomes the infection and the antibodies begin to appear in excess often is accompanied by a dramatic clinical change, which is recognized as a crisis. The alterations produced in permeability of membranes are qualitatively similar, whether produced by a bacterial infection, such as the Meningococcus, an extracellular infection, due to the nematode Trichinella, an intracellular infection caused by a Rickettsia, or an immune reaction occurring in the absence of actual infection, such as serum sickness.

PHYSICAL THERAPY

Trevor-Roper [251] reviews the value of physical therapy in ocular disease. Ultraviolet and infrared rays are of doubtful value for ocular conditions. There may be slight beneficial effect in phlyctenular disease, blepharitis, and iritis. There are other forms of therapy which are more efficacious.[252] Infrared radiation has little application in ophthalmology. It causes heating of tissues; it is more penetrating than surface heating but less than diathermy, and, as such, is sometimes convenient for ward treatments, since the hand infrared lamp is less cumbersome to carry and apply than is the diathermy machine. It has certain notorious ill-effects on the eye that discourage its use.

Electrolysis, a form of low-voltage electrotherapy, is of value for the destruction of follicles of ingrowing eyelashes, and perhaps can be used for xanthelasma and angioma. Galvanism is

249. Lodato, G.: Experimental Retinitis Pigmentosa Due to Sodium Iodate in Albino Rabbits, Gior. ital. oftal. **4**:226, 1951; Experimental Pigmentary Degeneration of the Retina in Rabbits Undergoing Filatov's Treatment, ibid. **4**:125, 1951.

250. Harrell, G. T., Jr., and Aikawa, J. K.: Alterations in Permeability of Membranes During Infections, J. A. M. A. **147**:232, 1951.

251. Trevor-Roper, T. D.: Present Status of Physiotherapy in Ocular Disease, Brit. J. Ophth. **35**:583, 1951.

252. Trevor-Roper.[251] Hoffmann, W.: A Lamp for the Ultraviolet Irradiation of the Anterior Segment of the Eye, Klin. Monatsbl. Augenh. **119**:41, 1951.

alleged to relieve pain in blepharospasm, and faradism may be used to stimulate mechanically embarrassed muscles that have an unimpaired nerve supply. Iontophoresis is of value in aiding penetration of drugs into the anterior segment of the globe. High-voltage therapy has considerable value in operative treatment as a coagulation or cutting diathermy.

The principal effect of medical diathermy is that of heating the tissues, with the great advantage that the heat may be concentrated at will in deeper tissues. The side-effects of the heating are capillary dilation, leucocytosis, relief of pain, and metabolic stimulation. In addition, there is lowering of the viscosity. The old-fashioned long-wave application, with direct contact of electrodes on the body, has given place, for technical, as well as therapeutic, reasons, to increasingly short waves, those of wave lengths between 3 and 30 meters being used generally. Short waves or microwaves are also available with wave lengths of 30 to 1 cm. and a frequency of 1,000 to 30,000 megacycles per second. However, as noted, this produces cataract experimentally, corneal opacities, and mydriasis. Trevor-Roper [251] states that for the relief of pain due to inflammation or congestive glaucoma, diathermy of this type is helpful. Superficial ulcers, deep keratitis, and episcleritis respond best. Particularly, there is relief of pain in cases of episcleritis.

Physical therapy is becoming less and less popular. The uncertainty of the effects, the difficulty of assaying statistically their results, and the likelihood of the patient's being psychologically impressed make the scientific ophthalmologist rather suspicious of reports concerning this form of therapy.

Good results have been obtained with beta radiation in preventing postoperative vascularization of the cornea after transplantation and in treatment of acne rosacea keratitis, corneal abscesses, recent burns, scleritis, and various forms of vernal conjunctivitis.[253]

ULTRAVIOLET IRRADIATION OF PLASMA

Ultraviolet irradiation of human plasma was introduced for sterilizing purposes after it was recognized that homologous-serum jaundice could be transmitted in this medium. There is evidence which attests to the efficacy of ultraviolet radiation in eliminating the virus of homologous-serum jaundice and to its safety. Recently it has been suggested by Cutler and co-workers [254] that alterations occur in the clotting mechanism of irradiated plasma. But Kaplan and Freedman [255] were unable to demonstrate any alteration in the clotting mechanism of fresh plasma after ultraviolet irradiation.

Two interesting reports of improvement following the use of ultraviolet radiation in uveitis have appeared within the past year.[256]

SUPERSONICS IN DIAGNOSIS

Because of their ability to penetrate tissues, high-frequency acoustic vibrations have found both diagnostic and therapeutic applications in medicine. The therapeutic applications have received most attention. The thermal, mechanical, and chemical changes produced by supersonic vibrations as they pass through tissues have been utilized in the treatment of a variety of diseases. The use of supersonic radiation in diagnosis may also be important. Alterations in density or elasticity of a tissue can be detected with the aid of supersonic waves. The tissue is exposed to the waves, and the supersonic echoes returning to the surface are studied; or the tissue is exposed to supersonic energy, and the amount which passes through the tissue is measured. The first method is based on the principle that supersonic waves passing through a medium are reflected back to the source as echoes when they encounter a surface "inter-

253. Paufique, L., and Rougier, J.: Treatment with Beta Rays in Ocular Disease, Ann. ocul. **184**:577, 1951.

254. Cutler, S. S.; Burbank, B., and Marzullo, E. R.: Hypocoagulability of Certain Irradiated Plasmas, J. A. M. A. **143**:1057, 1950.

255. Kaplan, S. R., and Freedman, I. A.: Effects of Ultraviolet Ray Irradiation on Clotting Mechanism of Plasma, J. A. M. A. **147**:229, 1951.

256. Rhoades, A. L.: Uveitis, Jackson Clin. Bull. **13**: Nov., 1951. Farmer, D. F.: Sullivan, C. P., and Sullivan, W. B.: The Use of Hemoirradiation (Knott Technique) in Eye Infections, at a meeting of the American Blood Irradiation Society, Atlantic City, N. J., June 9, 1951.

phase" of changing density within the medium. Thus, when the waves strike a tumor, a foreign body, or a collection of fluid within the tissue, some of them are reflected back to the surface as echoes. The intrinsic character of the echoes gives clues to the consistency of a lesion, and the time required for the echoes to return to the surface gives an indication of the depth of the lesion. With such a method, gallstones, intracranial neoplasms, and foreign bodies in animal tissues have been detected.[257] Wild and Neal[257a] have reported distinguishing between carcinomatous and noncarcinomatous tumors of the breast by this method. The supersonic-vibrations technique used by Wild and Neal employed an ultrasonoscope that was not quite as large as the bell of a stethoscope and could be applied to any part of the body surface.[257b]

Both the echo technique and the selective transmission method utilize supersonic vibrations of such short duration and low intensity that no symptoms are produced and no tissue alterations are detectable.

Supersonic therapy has been used in an effort to clear up vitreous opacities and after-hemorrhages and to promote the resolution of chalazia. The principal objection is the risk of causing the concussion cataract which has been observed to follow such treatment in experimental animals; since the physiologic effects are thought to be due to the heat generated, other established methods are presently preferred to supersonic methods.[258] (See radiation section for other ocular effects of ultrasonic waves.)

FEVER THERAPY

Pyromen,* a sterile nonprotein, nonanaphylactogenic bacterial component, is available as a stable colloidal dispersion for parenteral use. It is probably a complex polysaccharide and is of value in certain allergic dermatologic and ophthalmic disorders. The dose recommended ranges from 5 to 10 γ, injected two to three times a week. The initial dose of 1 or 2 γ is usually administered intravenously. Subsequent doses may be given intravenously or subcutaneously. The dose must be varied according to tolerance and clinical response. The dose has to be raised only when the patient fails to show evidence of response, such as clinical improvement, leucocytosis, or a mild constitutional febrile reaction. Less than the average adult dose should be used with aged or debilitated patients, but children can tolerate the adult dose. One should not exceed 5 γ in conditions in which fever is contraindicated. Occasional asthmatic attacks have been reported after its use. After the administration of pyromen* there is an increase in circulating leucocytes. Apparently, pyromen* stimulates the adrenal cortex. However, there is a difference. Corticotropin-induced leucocytosis is abolished in the dog by removal of the adrenal glands, whereas pyromen* given to dogs after adrenalectomy still induces a leucocytic response, but not to the same degree as would be observed in adrenal-intact animals. Certain activities of pyromen* appear to differ radically from those of cortisone. In rabbits the Arthus phenomenon, as elicited by crystalline egg albumin, is inhibited by cortisone, while it is enhanced, and the plasma antibody titer is elevated, by "pyromen."[259]

257. (*a*) Wild, J. J., and Neal, D.: Use of High Frequency Ultrasonic Waves for Detecting Changes of Texture in Living Tissues, Lancet **1**:655, 1951; (*b*) Experimental Application of Ultrasonics to the Localization of Brain Tumors, J. Neurosurg. **8**:198, 1951. (*c*) Ultrasonics in Diagnosis, editorial, J. A. M. A. **146**:1033, 1951.

258. Belz and Bouchel.[186a] Belz.[186b] Hallermann and others.[187a] Krusen.[187b] Lavine.[188]

259. (*a*) Stuart, E. G.: Accelerating Effect of Pyromen in Contrast to Inhibitory Effect of Cortisone on Arthus Phenomenon in Rabbits, Federation Proc. **10**:133, 1951; (*b*) Accelerating Effect of Pyromen in Contrast to Inhibitory Effect of Cortisone on Arthritis Phenomenon in Rabbits, Am. J. M. Sc. **221**:470, 1951. (*c*) Clemente, C. D.; Chambers, W. W.; Greene, L. C.; Mitchell, S. Q., and Windle, W. F.: Regeneration of the Transected Spinal Cord of Adult Cats, Anat. Rec. **109**:280, 1951. (*d*) Zindler, G. A.: Pyromen therapy in the Treatment of Food Allergy, Ann. Allergy **9**:494, 1951. (*e*) Wittich, F. W.: Pyromen in the Treatment of Perennial Respiratory Allergies, ibid. **9**:502, 1951. (*f*) Clemente, C. D.: Production of Periods of Leukocytosis and Tolerance of Consecutive Oral Administration of Different Bacterial Pyrogens, Federation Proc. **10**:27, 1951. (*g*) Soylemezogou, B., and Wells, J. A.: Comparison of Leukocyte Response to ACTH and Bacterial Pyrogen, Proc. Soc. Exper. Biol. & Med. **77**:43, 1951.

Administration of pyromen® produces inhibition of the formation of glial scars and reduction in the amount of collagenous scarring.[259b]

It has been shown that fever is unnecessary for the beneficial effects of pyromen® therapy.[259c]

Alvis [260] states that the mechanism by which the beneficial effect of hyperpyrexia is achieved is not completely understood. It is essentially a stimulation of the natural defense reaction. Some of the physiologic effects which one sees upon the use of fever therapy are as follows: (1) dilatation of peripheral arterioles and capillaries; (2) accelerated circulation (volume flow increased up to 400%); (3) increased metabolic rate up 7% for each degree (F.) of increase; (4) increased white blood cell count by stimulation of the hematopoietic system; (5) increased phagocytosis (leucocytes move faster; fixed phagocytic cells are more voracious); (6) variation in sedimentation rate as clinical improvement occurs; (7) increased pulse and respiratory rates; (8) increased pulse pressure through lowering of diastolic level; (9) increased activity of such vital glands as the thyroid and adrenals, (10) increased production of hormones—corticotropin, cortisone, etc.

Alvis also believes that foreign-protein injections may stimulate some of the resistance factors without fever, but such injections as do induce fever are more effective, their efficacy being proportional to the degree and duration of the fever. Hyperpyrexia alone as produced by physical means will accelerate all the defense reactions more effectively than injection of any pyrogen.

Newell [261] describes the action of pyrogens and stresses that, although much of their effect is due to adrenocortical stimulation, there are other important actions. The occasional prompt beneficial effect of pyrogens when corticotropin and cortisone have failed may be due to these actions.

Wolffersdorff reports definite benefit from "pyrifer" therapy in optic and retrobulbar neuritis and in optic atrophy.[262]

FLUORESCEIN

Fluorescein has been used in detecting the permeability of the lacrimal passage and in measuring the permeability of the blood-aqueous barrier.[263]

In tests of the lacrimal passages for permeability, the patient sits upright, holding the head straight, and a cotton-wool pledget on a holder is introduced under the inferior concha in the nose. Then a little 1% fluorescein sodium is placed in the conjunctival cul-de-sac. After five minutes the pledget holder is taken out of the nose; if the pledget is found untinged, the patient is made to sneeze with open nostrils. If there is still no trace of fluorescein in the nasal secretion, a drop of 1:1,000 epinephrine hydrochloride solution is put in the conjunctival cul-de-sac, and the subject is made to sneeze five minutes later. If this test still gains a negative result, the lacrimal passages must be syringed in order that one may be certain that there is no obstruction. The younger the patient, the greater the likelihood that patency will be established by a simple application of fluorescein in the cul-de-sac. The older the patient, perhaps the less frequent the blinking and, therefore, the less the likelihood of obtaining seepage in this way.

Miller and Swanljung [263c] describe a study of the entrance of fluorescein into the anterior chamber of the eye in patients with glaucoma. They found no diagnostic value attributable to the fluorescein test in simple and congestive glaucoma. The entrance of fluorescein into the eye is unaltered by the spontaneous changes in tension so characteristic of both these types of glaucoma. However, fluorescein enters the eye more readily in the presence of active iridocy-

260. Alvis, V. Y.: The Role of Hyperpyrexia in the Management of Ocular Inflammatory Disease, Am. J. Ophth. **34**:1741, 1951.

261. Newell, F.: Foreign Protein Therapy in Ophthalmology, Am. J. Ophth. **34**:1189, 1951.

262. Wolffersdorff, H. V.: "Pyrifer" Therapy in Different Optic Nerve Affections in the Period 1939-1950, Klin. Monatsbl. Augenh. **119**:271, 1951.

263. (*a*) Huck, H.: Usefulness of Fluorescein in Testing the Permeability of the Lachrymal Passage, Ophthalmologica **121**:110, 1951. (*b*) Hager, H.: A Simple Apparatus for Fluorescein Measurements in the Anterior Chamber, Klin. Monatsbl. Augenh. **119**:81, 1951. (*c*) Miller, S. J. H., and Swanljung, H.: Appearance of Fluorescein in the Aqueous of Glaucomatous Eyes, Brit. J. Ophth. **35**:356, 1951.

clitis, irrespective of the presence or absence of glaucoma. Therefore, it may be of value in distinguishing secondary glaucoma from other varieties. When the iridocyclitis ceases to be active, the fluorescein curve may revert to normal levels; so the test is of little value in the diagnosis of glaucoma secondary to inactive iridocyclitis. Miotics also alter the penetrability of fluorescein.

Fluorescein has been employed for localization of neoplasms, particularly the radioactive form (see radiation section).

HYPERTHYROIDISM

Many articles have been written during the past year concerning the therapy of malignant exophthalmos, as well as the less progressive varieties which are associated with thyroid disease.[264] Beneficial effects in malignant exophthalmos have been described from the use of estrogens, irradiation of the pituitary, and the use of thyroid. However, a number of failures have also been reported. Weekers and Dedoyard [264i] did not note any good effect from estrogens, thyroid, or irradiation of the pituitary gland.

Experimental work by Asboe-Hansen and Iversen [265] suggests that the changes in the organism following the thyrotropic type of exophthalmos are attributable to a general systemic change, and not to a special phenomenon in the orbit. Exophthalmos was produced in guinea pigs by the injection of thyrotropic hormone. In one-half the animals the thyroids were removed; in the other half they were not. Results show that the retrobulbar fat was replaced by a loose connective tissue containing increased amounts of mucopolysaccharides, presumably hyaluronic acid. Similar changes were found in peritesticular, perirenal, and axillary fat. It appears that thyrotropin administered in large doses causes a rapid mobilization of the fatty tissues from the normal reservoirs and that connective tissue with newly formed hyaluronic acid replaces the fatty tissue. Owing to the marked ability of mucopolysaccharides to bind water, the orbital tissues will be more voluminous, so that exophthalmos develops.[265]

Investigators continue to explore the possibilities of radioactive iodine in treatment of hyperthyroidism.[265] Barnum and his co-workers [266] describe a diffuse sensitivity reaction to thiouracil therapy in hyperthyroidism. This reaction closely resembled periarteritis nodosa with associated Raynaud's phenomenon.

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264. (*a*) Woods, A. C.: The Ocular Changes of Hyperthyroidism, West. J. Surg. **59**:288, 1951. (*b*) Medine, M. M.: Malignant Exophthalmos, Am. J. Ophth. **34**:1587, 1951. (*c*) Beierwaltes, W. H.: Irradiation of the Pituitary in Treatment of Malignant Exophthalmos, J. Clin. Endocrinol. **11**:512, 1951. (*d*) Van Manen, J. G.: Exophthalmic Ophthalmoplegia, Ophthamologica **122**:207, 1951. (*e*) Hermann, K.: Pituitary Exophthalmos: An Assessment of Methods of Treatment, Brit. J. Ophth. **36**:1, 1952. (*f*) Cope, O.: Diseases of the Thyroid, New England J. Med. **246**:408; 368; 451, 1952. (*g*) Wing, E. S., and Asper, S. P., Jr.: Propyl Thiouracil in Hyperthyroidism, Bull. Johns Hopkins Hosp. **92**:1, 1952. (*h*) Mann, I.: A Further Report on Exophthalmic Ophthalmoplegia and Its Relation to Thyrotoxicosis, Am. J. Ophth. **34**:960, 1951. (*i*) Weekers, R., and Dedoyard, J.: Endocrine Exophthalmos, Boll. Soc. belge opht. **97**:122, 1951.

265. Asboe-Hansen, G., and Iversen, K.: Influence of Thyrotropic Hormone on Connective Tissue: Pathogenetic Significance of Mucopolysaccharides in Experimental Exophthalmos, Acta endocrinol. **8**:90, 1951.

265a. Duffy, B. J., Jr., and Howland, J. W.: Radio-Iodine Principles of Diagnosis and Treatment of Thyroid Disease, New York J. Med. **51**:1399, 1951. Portmann, U. V.; Hayes, R. A.; McCullagh, E. P., and Richards, C. E.: Experiences in Treatment of Diseases of Thyroid with Radioactive Iodine, Am. J. Roentgenol. **66**:179, 1951. Scott, W. G.; Seaman, W. B.; MacBryde, C., and others: Observations and Results in Treatment of Hyperthyroidism with Radioactive Iodine (I^{131}), ibid. **66**:171, 1951. Crile, G., Jr., and McCullagh, E. B.: Treatment of Hyperthyroidism, Ann. Surg. **134**:18, 1951.

266. Barnum, D. I.; De Takets, G., and Dolkart, R. E.: Periarteritis Following Thiouracil Therapy of Hyperthyroidism, Angiology **2**:256, 1951.

The use of antithyroid drugs in pregnancy is summarized by Astwood.[267] Catz, Petit, and Starr [268] describe a series of 26 hyperthyroid patients, 22 of whom responded to sodium 5-iodo-2-thiouracil. This substance has the advantage over the older thiouracil preparations in producing a more rapid response and in the abscence of a goiterogenic effect.

D'Angelo, Paschkis, Gordon, and Cantarow [269] describe an ingenius method for determining the thyroid-thyrotropic hormone balance in the blood.

Several workers have described benefit in cases of simple toxic diffuse goiter disease from the use of estrogens.[270]

CHONDROITIN SULFATE

Chondroitin sulfate is one of the important constituents of cartilage, as it is believed that cartilage contains chondroitin sulfate and the insoluble protein collagen. Chondroitin sulfate is a nonreducing polysaccharide composed of equal parts of amino sugar and acetic, sulfuric, and glucuronic acids. The sulfuric acid is present in an esterified form. It has been shown that the administration of radioactive sulfur in the form of sulfate causes deposition of radioactivity in the knee-joint cartilage of weanling rats. In addition, the radioactivity was concentrated in the chondroitin sulfate isolated from the cartilage.[271] It has also been shown by Deziewiatowski [271a] that thiouracil depresses the amount of sulfate found in the knee-joint cartilage and that thyroxin increases the amount deposited; in other words, thyroxin counteracts the depression of deposition produced by thiouracil.

MIGRAINE THERAPY

It has been suggested by the studies of Campbell, Hay, and Tonks [272] that in the early stages of migraine the blood sodium rises to a high level and, at the same time, there is a marked hydration of the blood. This may be due to dysfunction of the adrenal cortex and the posterior lobe of the pituitary gland.

The large number of therapeutic agents which are currently used in the treatment of migraine indicates that at present no single drug will relieve all patients and that there is no specific preventive measure or medication.[273] Many theories have been proposed to explain the cause of this condition.[274] It is believed that the headaches may be precipitated either by too rapid cerebral vasodilatation or by too rapid vasoconstriction, thus producing a change in the caliber of the blood vessel. It is this factor which makes possible effective use of both vasoconstrictors and vasodilators in the treatment of migraine. Therapy is usually classified under the following four methods, singly or in combination: pharmacotherapy, physical therapy, surgery, and psychotherapy. The drugs commonly used in the treatment of migraine fall into three main categories: ergotamine and derivatives, vasodilators, and analgesics, and, perhaps one should add, adrenergic-blocking agents, of which the ergotamine and derivatives may be examples. These agents have been listed in Table 6.[273b]

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267. Astwood, E. B.: Use of Antithyroid Drugs During Pregnancy, J. Clin. Endocrinol. **11**:1045, 1951.

268. Catz, B. D.; Petit, D. W., and Starr, P.: Sodium 5-Iodo-2-Thiouracil in Treatment of Hyperthyroidism, J. Clin. Endocrinol. **11**:978, 1951.

269. D'Angelo, S. A.; Paschkis, K. E.; Gordon, A. S., and Cantarow, A.: Thyroid-Thyrotropic Hormone Balance in the Blood of Normal and Endocrinopathic Individuals, J. Clin. Endocrinol. **11**:1237, 1951.

270. Okie, M. B.; Denee, H. B., and Daley, W.: Estradiol Implants and Postoperative Pituitary Exophthalmos, J. Internat. Coll. Surgeons **16**:98, 1951. Francois, J.: Estrogen Therapy in Graves' Disease, Bull. Soc. belge opht. **97**:194, 1951.

271. Deziewiatowski, D. D.: Chondroitin Sulfate, J. Biol. Chem. **189**: (*a*) 187; (*b*) 717, 1951.

272. Campbell, D. A.; Hay, K. M., and Tonks, E. M.: An Investigation of the Salt and Water Balance in Migraine, Brit. M. J. **2**:1424, 1951.

273. Simidu, S.: (*a*) On Treatment of True Migraine, Acta Soc. Ophth. Jap. **55**:121, 1951; (*b*) Migraine Therapy, Department of Pharmacy, Philadelphia College of Pharmacy and Science, Philadelphia Med. **47**:905, 1952.

274. Campbell, Hay, and Tonks.[272] Simidu.[273a] Editorial.[273b]

CHEMOTHERAPEUTICS OF NEOPLASTIC DISEASE [275]

A vigorous search has been directed toward the uncovering of chemical substances which may be of therapeutic value in neoplastic diseases. The size of the growing literature attests to the importance of this work. Since neoplasms perhaps have a uniform biochemical pattern, one might anticipate that a chemical might be expected to act effectively as an antineoplastic substance. At present we are going through a period of temporary enthusiasm for any new agent, followed by general acceptance of the lack of value of the compound. We are still at a great distance from the ideal agent. Hormones, nitrogen mustard, radioactive iodine, phosphorus, urethan, potassium arsenite solution N. F. (Fowler's solution), all have some beneficial

TABLE 6.—*Drugs Used in Treatment of Migraine*

Medication	Route of Administration	Dosage Schedule
Ergotamine tartrate (1 mg.) and caffeine (100 mg.) (ergotamine with caffeine; cafergot®)	Oral	Two tablets at first sign of headache; then 1 every half-hour up to total of 6 tablets if necessary
Ergotamine tartrate	Intramuscular	0.5-1.0 mg. at onset; dose repeated in 1 or 2 hr. if needed
	Oral	4-5 mg. at onset; then 2 mg. each half hour until relief or until total of 10 mg. has been taken
Dihydroergotamine (DHE-45)	Intravenous or intramuscular	0.5-2.0 mg. given at time of an attack (usual dose 1 mg.)
Ergotamine tartrate (2 mg.), "bellafoline" * (0.25 mg.), caffeine (100 mg.)	By suppository	One at onset of headache; repeated in half-hour if necessary up to a total of 3
Nicotinamide	Intramuscular or intravenous	100 mg. promptly at onset of headache
Codeine phosphate	Oral	60 mg., followed by complete bed rest for several hours
Acetylsalicylic acid	Oral	0.3-0.6 gm. at onset; dose repeated in 15 min., then every half-hour to 6 doses
Acetylsalicylic acid (0.3 gm.), caffeine (0.1 gm.)	Oral	Two capsules at onset; then 1 every hour up to 6 capsules
Acetylsalicylic acid (0.3 gm.), amobarbital (0.1 gm.)	Oral	Two capsules at onset; then 1 every half-hour up to 6 capsules

* "Bellafoline" is the malic acid salts of the total levorotatory alkaloids of belladonna leaves.

275. (*a*) Nettleship, A.: Chemotherapeutics of Cancer, Current M. Dig. **19**:46, 1952. (*b*) Code, J.: Chemotherapy in the Treatment of Malignant Disease, Brit. M. J. **2**:1193, 1949. (*c*) Haddow, A.: The Chemotherapy of Cancer, Practitioner **167**:36, 1951. (*d*) Udupa, K. N.: Present Status of Chemotherapy in Certain Malignant Diseases, Antiseptic **49**:126, 1952. (*e*) Inactive Compounds in Tumor Chemotherapy, Announcement, Cancer Res. **12**:241, 1952. (*f*) Golden, A.; Greenspan, E. M., and Schoenbach, E. B.: Studies on the Mechanism of Action of Chemotherapeutic Agents in Cancer, Cancer **5**:153, 1952. (*g*) Iversen, K., and Meulengracht, E.: Oral Treatment of Polycythema Vera with Beta-Naphthyl-Di-2-Chloroethylamine (R48), Brit. M. J. **2**:510, 1951. (*h*) Buckley, S. M.; Stock, C. C.; Crossley, M. L.; Rhoads, C. P.; Patti, J., and Sata, E. S.: Inhibition of Crocker Mouse Sarcoma, Cancer **5**:142, 1952. (*i*) Bayrd, E. D.; Stickney, J. M.; Hall, B. E., and Watkins, C. H.: Clinical Observations on the Use of Triethylenemelamine, ibid. **5**:336, 1952. (*j*) Karnofsky, D. H.; Burchenal, J. H.; Armistead, G. C., Jr.; Southam, C. M.; Bernstein, J. L.; Craver, L. F., and Rhoad, C. P.: Triethylene Melamine in the Treatment of Neoplastic Disease, A. M. A. Arch. Int. Med. **87**:477, 1951. (*k*) Meyer, L. M.; Beyers, M. R.; Sawitsky, A.; Brahn, C., and Ritz, N. D.: Treatment of Lymphomata with Triethylene Melamine, Cancer Res. **11**:268, 1951. (*l*) Nathanson, I. T., and Kelley, R. M.: Hormonal Treatment of Cancer, New England J. Med. **246**:180, 1952; 135, 1952. (*m*) Luttgens, W. F., and Bayard, E. D.: Treatment of Multiple Myeloma with Urethane, J. A. M. A. **147**:824, 1951. (*n*) Silverberg, J. H., and Dameshek, W.: Use of Triethylene Melamine in Treatment of Leukemia and Leukosarcoma, ibid. **148**:1015, 1952. (*o*) Oncolytic Action of Epinephrine, editorial, ibid. **147**:578, 1951. (*p*) Lewis, M. R., and Aptekman, P. M.: Inhibitory Action of Adrenal on Growth of Rat Sarcoma, Science **113**:557, 1951.

effect. Over 5,000 such compounds have been tested to date. The most recent agents have ranged from bacterial toxins to complex hormones. The use of colloidal sols containing radioactive gold and manganese is still in the experimental stage. Enzymes have been used; extracts of various tissues, amino acids, urethan, and epinephrine have all been tried. A number of carcinogenic chemicals are being tested, undoubtedly on the basis of the reasoning that since x-rays both cure and cause tumors, chemotherapeutic agents may do likewise. Caloric intake has been restricted in the hope of starving the tumor, and not the patient. Androgens and estrogens now have an established place in the chemotherapy of prostate and breast carcinoma. Antifungicides, antibacterial agents, and antiviral agents have been used in these studies. The nitrogen mustards have been found to be palliative against lymphadenopathy, fever, and some symptoms in patients with Hodgkin's disease who have no longer responded to x-rays. The treatment has many undesirable features. Patients are often nauseated, vomit, and manifest leucopenia, thrombocytopenia, and severe anemia. Normal tissue, as well as neoplastic tissue, is damaged by nitrogen mustard. One may see hyperplasia of bone marrow and atrophy of seminiferous tubules. After repeated use, nitrogen-mustard therapy loses its effectiveness.

Folic-acid antagonists have been tried, with some measure of success, in the chronic leukemia group, but are limited in their use by virtue of toxic symptoms. There is not enough margin of safety between the damage of malignant tissue and that of normal tissue to allow the successful use of many of these chemotherapeutic agents. Urethan has had a profound cytologic influence. It is shown to be carcinogenic, and yet has found increasingly widespread use in the therapy of various neoplasms. It is questionable whether it has any real therapeutic effect.

Considerable interest has been aroused recently by the development of two compounds related to nitrogen mustard which are effective when given orally. The first, β-naphthyl-di-2-chloroethylamine (R48),[275e,f] and the second, 2,4,6-triethylenimino-*s*-triazine, or triethylene melamine.[275i]

One may divide these agents into two groups: (1) those that change the host so that the tumor cannot grow, an example of which is diethylstilbestrol, in prostatic carcinoma, and (2) those that have a lethal action on tumor cells, characteristic of which are the nitrogen mustards, aminopterin (4-aminopteroylglutamic acid), and methane.[275a–m]

STREPTOKINASE AND STREPTODORNASE

A number of investigators have reported on the use of streptokinase and streptodornase in the treatment of serous, purulent, and hemorrhagic exudates. These agents were used when they could be brought into direct contact with fibrin or pus for a sufficiently long period. They have been particularly helpful in cases of hemothorax.[276] Jukofsky's[276h] studies are interesting in this regard. He reports the clearing of rabbit blood from the anterior chamber of rabbit eyes by a simultaneous injection of 50,000 units of streptokinase with the introduction of the blood. It was his impression that this procedure produced clearing more rapidly than in the control eyes, and that when used in this concentration streptokinase produced no local damage to the anterior chamber. However, higher concentrations produced clouding of the cornea and iritis. Drop instillations of 200,000 units of streptokinase on the anterior surface

276. (*a*) Morrell, C., and Weinberg, J. A.: Streptokinase and Streptodornase in Suppurative Lesions, West. J. Surg. **59**:524, 1951. (*b*) Mienster, J. T.; Flance, I. J., and Sweeney, B.: Treatment of Unresolved Pneumonia with Streptokinase and Streptodornase, Am. J. Med. **12**:376, 1952. (*c*) Sherry, S., and Tillett, W. S.: The Local Use of Streptokinase and Streptodornase in Chronic Refractory Areas of Suppuration with Draining Sinuses, Ann. Surg. **135**:479, 1952. (*d*) Wright, L. T.; Smith, D. H.; Rothman, M.; Metzger, W. I., and Quash, E. T.: Use of Streptokinase-Dornase in Certain Surgical Conditions, J. Internat. Coll. Surgeons **15**:286, 1951. (*e*) McVay, L. V., Jr., and Sprunt, D. H.: Streptokinase and Streptodornase in the Treatment of Diabetic Gangrene, A. M. A. Arch. Int. Med. **87**:551, 1951. (*f*) Hubbard, W. M., Jr.: Systemic Toxic Responses of Patients to Treatment with Streptokinase, Streptodornase, J. Clin. Invest. **30**:1171, 1951. (*g*) Adie, G. C., and Childress, W. G.: Experiences with Streptokinase and Streptodornase, Ann. Surg. **134**:659, 1951. (*h*) Jukofsky, S. L.: A New Technique in the Treatment of Hyphemia, Am. J. Ophth. **34**:1692, 1951. (*i*) Prevention of Operative Adhesions, editorial, J. A. M. A. **145**:1138, 1951.

of the eye produced no pathologic effects except diffuse injection of the conjunctiva. Administered subconjunctivally, streptokinase produced considerable discomfort, which persisted several days. Rapid disappearance of the subconjunctival hemorrhage was reported after the topical use of streptokinase. In a case of hyphema in the anterior chamber of a boy of 9 years, intracameral injection of streptokinase after paracentesis and withdrawal of bloody aqueous resulted in disappearance of the blood in less than two hours. However the patient had bloodstaining of the cornea. This paper is a preliminary and limited report, and further studies will have to be carried out before the use of these agents in ophthalmology can be properly evaluated.

Toxic signs following the use of streptokinase and streptodornase in pulmonary disease have consisted of fever, associated leucocytosis, and sometimes glycosuria and proteinuria. The causes of the reactions are not certain, but foreign materials present in the solution or the breakdown products of their enzymatic action may be responsible. The addition of antibiotics to the enzyme solution may aid in reduction of infection in purulent processes and contamination in uninfected collections of blood. As noted previously in this review, the use of streptokiase and streptodornase may facillitate the spread of infection by breaking down barriers which previously localized the infectious process. These agents can also be employed for the prevention of postoperative adhesions.[276]

A mixture of streptokinase, 100,000 units, and streptodornase, 25,000 units, is now available commercially ("varidase"). In addition to streptococcic enzymes, crystallized trypsin, obtained from the pancreatic tissue of animals, is being used topically in a similar manner ("tryptar").

HYALURONIDASE

Since the demonstration of Duran-Reynals that dermal spread of vaccinia could be greatly increased by testicular extract, the mechanism of this phenomenon has received considerable attention. Although the reaction has been repeatedly demonstrated for the dermotropic viruses, similar effects on the influenza group of viruses have not been shown. Hyaluronidase of streptococcic and pneumococcic origin, and alidase,[9] hyaluronidase of testicular origin, failed to influence infectivity of the influenza virus when injected into the allantoic cavity.[277] Hyaluronidase has been shown to block inflammatory reaction of the skin to many irritants.[278]

Since one of the causes of chronic ulcer is inadequate nutrition to the tissues, Ende believed that hyaluronidase [279] might facilitate the passage of necessary agents into an ulcerated area and thereby promote healing. His experience in a few cases suggested that this agent might be helpful in wound healing.

OCULAR WOUND HEALING

Dunnington and Regan [280] studied histologically experimentally induced wounds and found that those treated with thrombin showed some interference with apposition of the wound edges. This observation led the authors to conclude that, with its very limited tensile strength, thrombin was not an ideal material with which to insure adequate closure of ocular wounds. However, a recent presentation by Tassman, DeLong, and Hallett [281] showed histologic evidence of no interference with fibroblastic proliferation by thrombin and fibrin as they employed these agents.

Additional evidence has been presented showing the value of various amino acids on the healing of superficial and deep corneal wounds. The speed of cicatrization was increased particularly by arginine, histidine, and cysteine, while the effect of tryptophan and proline

277. Fastier, L. B.: Failure of Hyaluronidase to Influence Growth of Pr 8 Virus in Chick Embryos, J. Immunol. **66**:1, 1951.

278. Di Caprio, J. M.; Rantz, L. A., and Randall, E.: Studies on Streptococcal Hyaluronidase and Antihyluronidase, A. M. A. Arch. Int. Med. **89**:374, 1952. Glassman, J. M.; Blumenthal, A.; Beckfield, W. J., and Seifter, J.: Effect of Hyaluronidase in Inflammatory Response to Primary Irritants, Federation Proc. **11**:348, 1952.

279. Ende, M.: Use of Hyaluronidase in Chronic Ulcers, South. M. J. **44**:661, 1951.

280. Dunnington, J. H., and Regan, E. F.: Ocular Wound Healing, Am. J. Ophth. **35**:167, 1952.

281. Tassman, I.; DeLong, and Hallett: Fibrin and Thrombin in Ocular Wound Healing: Histological Study, read before the Fourth Wills Clinical Conference, March 20, 1952.

was slight.[282] Swan carefully and thoroughly reviews the treatment of corneal disease and corneal wounds.[283] He calls attention to the importance of the vehicle employed for the administration of drugs for diseases of the cornea, as do Hind and Goyan [284] and Mims.[285] Bell [286] suggests the use of cetyldimethylbenzylammonium chloride as a preoperative irrigating solution of the conjunctival cul-de-sac. This substance is known as zettyn,® and he recommends that it be used in a strength of 1:10,000.

RUTIN AND SIMILAR COMPOUNDS

Evidence is presented by Schiller that the administration of rutin intravenously, 50 to 75 mg. per kilogram of body weight, acts as a strong primary cutaneous vasoconstrictor and increases vasoconstriction produced by epinephrine. It is possible, therefore, that the effects of the vitamin-P flavinoids on capillary fragility may be related to their ability to constrict minute blood vessels strongly, rather than to a permeability factor in itself. It would appear, at least, that one of the important anti-capillary-fragility factors may be not a chemical substance, but merely a physical state of sustained minute-vessel constrictor tone.[287]

Quercetin and quercitrin exert the same physiologic effects as rutin, and are not any more toxic than rutin.[288] It has been shown by Griffith and Couch that rutin inhibits the capillary injury produced by alpha radiation in rats.[289] Investigations on the effect of rutin on diabetic retinitis and other ocular conditions have not shown any consistently favorable results.[290]

DIABETES MELLITUS, OCULAR CHANGES, AND THERAPY

It is encouraging in this day, when we are unimpressed with the therapy of diabetic retinopathy, to read Joslin's survey [291] of patients with diabetes of 24 years' duration. Although only a few of these persons were in perfect health, approximately 80% were still active. The patients who were in perfect condition were, with hardly an exception, those whose treatment had been initiated with strenuous control of the diabetes in their early years. This control was maintained for 10 years, more or less, to an extent much greater than usual, and even after the 10-year period a rigorous control was continued. In Joslin's opinion the evidence is overwhelming that strict treatment of diabetes pays and, moreover, that control of diabetes is possible. Of 114 patients in this group, 49% showed retinal arteriosclerosis, and 50% had retinal hemorrhages. About 50% of this 50% also showed exudates.

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282. De Berardinis, E., and Bonavolontà, G.: Healing Activity of Some Amino Acids on Experimental Corneal Lesions and Their Influence on Corneal Metabolism, Gior. ital. oftal. **4**:86, 1951.

283. Swan, K. C.: Symposium: Corneal Diseases: Treatment, Tr. Am. Acad. Ophth. **55**:387, 1951.

284. Hind, H. W., and Goyan, F. M.: New Concept of the Role of Hydrogen Ion Concentration and Buffer Systems in Preparations of Ophthalmic Solutions, J. Am. Pharm. A. (Scient. Ed.) **36**:33, 1947.

285. Mims, J. L.: Methyl Cellulose Solution for Ophthalmic Use, A. M. A. Arch. Ophth. **46**:644, 1951.

286. Bell, R. P., Jr.: A New Ophthalmic Irrigating Solution, Am. J. Ophth. **34**:1321, 1951.

287. Schiller, A. A.: Rutin-Potientation of Epinephrine, Am. J. Physiol. **165**:293, 1951.

288. Ambrose, A.; Robbins, D. J., and DeEds, F.: Comparative Toxicities of Quercetin and Quercitrin, J. Am. Pharm. A. (Scient. Ed.) **41**:119, 1952.

289. Griffith, J. Q., Jr., and Couch, J. F.: Inhibition by Rutin of Capillary Injury by Alpha-Radiation in Rats, Blood **6**:552, 1951.

290. Arriga Cantullera, J.: Rutin and Bishydroxycoumarin in Ophthalmology, Arch. Soc. oftal. hispano-am. **11**:373, 1951. Gördüren, S., and Tangun, A.: Rutin in Ophthalmology, Gáz. Klin. **9**:55, 1951. Palmer, L. J.; Flaherty, N. F.; Crampton, J. H., and Johnson, R. H.: Influence of Rutin upon Diabetic Retinitis, Northwest Med. **56**:69, 1951.

291. Joslin, E. P.: Status of Living Diabetics with Onset Under 40 Years of Age, J. A. M. A. **147**:209, 1951.

The constant search for better treatment of this progressive condition still goes on. A number of papers stress the importance of adequate control.[292] Others seek for other methods of improving the condition of those who failed to respond in spite of adequate control.[293] Lipotropic agents [293b] and gonadotropic hormones have been tried, with some reported success, in very small series 293.[a] On the other hand, Saskin, Waldman, and Pelner [294] reported beneficial results in diabetic retinopathy, from the use of testosterone propionate.[294] Cholst and his co-workers [295] employed retinal-vessel response to systemically administered benzazoline as a means of classifying diabetic change in the fundus. They found that 11 of 12 patients with no widening of the angioscotoma after intravenous injection of benzazoline were found to have diabetic exudates. The authors, therefore, suggest the possibility that the presence of exudates in the retina in diabetics is a manifestation of advanced vascular damage and that the presence of exudates offers the poorest prognosis so far as the regional retinal vessels and surrounding retinal areas are concerned.[296]

Zubrod and his co-workers [297] noted that in diabetics with Kimmelsteil-Wilson lesions the diabetes showed definite amelioration and acidosis was rare.

The chief distinction between protamine zinc insulin and NPH insulin is that the former is an amorphous material containing a variable quantity of protamine, 1.25 to 1.5 mg. per 100 units, which is sufficient to provide an excess, while NPH insulin is a crystalline product in which the protamine is completely combined with insulin. After injection, the action of NPH insulin starts in 2 hours, reaches a maximum in 10 to 20 hours, and is complete within 28 to 30 hours.[298]

Rodriquez [299] noted that cataract developed in pancreatectomized diabetic rats maintained on a high-carbohydrate diet. The incidence of the cataract development was less on a high-protein diet, and no cataracts at all were noted in these animals on a high-fat diet. Use of insulin prevented the onset of the cataract formation. In these experimental animals Rodriquez was able to correlate the incidence of the cataract with the severity of the disease, that is, the hyperglycosuria and the duration of the diabetes, and to relate it inversely to the age of the rats.

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292. Joslin.[291] Wilson, J. L.; Root, H. F., and Marble, A.: Prevention of Degenerative Vascular Lesions in Young Patients by Control of Diabetes, Am. J. M. Sc. **221**:479, 1951. Lawrence, R. D.; Scott, G. I.; Ashton, N.; Whittington, T. H.; Martin, M. M., and Oakley, W. G.: Discussion on Diabetic Retinopathy, Proc. Roy. Soc. Med. **44**:742, 1951. Sherrill, J. W.: Diabetic Retinitis, Bull. Scripps Metabolism Clinic **2**: 1951. Spoont, S.; Dyer, W. W.; Day, R., and Balzer, H.: Incidence of Diabetic Retinopathy Relative to the Degree of Diabetic Control, Am. J. M. Sc. **221**:490, 1951. Bell, E. T.: A Postmortem Study of 1,214 Diabetic Subjects with Special Reference to Vascular Lesions. Proc. Am. Diabetes A. **10**:62, 1950. Sheppard, L. B.: Diabetic Retinopathy, Quart. Rev. Ophth. **7**:3, 1951. Kennedy, R. J., and Kirschbaum, F. M.: Ocular Fundus Findings in 133 Cases of Diabetes Mellitus, Cleveland Clin. Quart. **18**:134, 1951. Post, L. T., and Stickle, A. W., Jr.: Fundus Changes in Juvenile Diabetics, Am. J. Ophth. **34**:1119, 1951. Panepinto, V.: Clinical and Anatomical Considerations in the Problem of Diabetic Retinopathy, Ann. ottal. e clin. ocul. **77**:233, 1951.

293. (*a*) Gronberg, A., and Svanteson, G.: Diabetic Retinopathy Improved by Gonadotrophic Hormones, Svenska läk-tidning. **48**:2005, 1951. (*b*) Desvignes, P., and Sadoughi, G.: Trial of Treatment of Diabetic Retinitis with Lipocaic Hormone, Bull. Soc. opht. France **2**:126, 1951.

294. Saskin, E.; Waldman, S., and Pelner, L.: Diabetic Retinopathy, Am. J. Ophth. **34**:613, 1951.

295. Cholst, M. R.; Schilback, H. F.; Handelsman, M. B., and Levitt, L. M.: Response of Retinal Vessels to Priscoline in Various Vascular Conditions, Am. J. Ophth. **35**:191, 1952.

296. Cholst, M. R.; Schilback, H. F.; Handelsman, M. B., and Levitt, L. M.: Response of the Retinal Vessels to Priscoline in Diabetes Mellitus, Am. J. Ophth. **35**:375, 1952; footnote 295.

297. Zubrod, C. G.; Eversole, S. L., and Dana, G. W.: Amelioration of Diabetes and Striking Rarity of Acidosis in Patients with Kimmelsteil-Wilson Lesions, New England J. Med. **245**:518, 1951.

298. Swallow, K. A., and Chute, A. L.: NPH Insulin, Canad M. A. J. **65**:23, 1951. Jameson, M.; Lacey, A. H., and Fisher, A. M.: NPH Insulin, ibid. **65**:20, 1951.

299. Rodriquez, R. R.: Influence of Diet and Insulin on the Incidence of Cataracts in Diabetic Rats, Yale J. Biol. & Med. **24**:103, 1952.

VITAMINS

Beneficial Results from Vitamin Therapy.—Vitamins have been found helpful in keratomalacia, corneal and conjunctival damage, and delayed wound healing after exposure to x-rays.[300] Helenien or adaptionol has improved dark adaptation.[301] Administration of the vitamin B complex by injection partly counteracts loss of cone function due to the action of trimethadione.[302]

Harmful Results from Use of Vitamins.—Fourteen cases of chronic vitamin-A poisoning have been reported since 1944.[303] Observers have noted the following characteristic manifestations: external cortical thickening of the affected bones, pain and swelling of the long bones, irritability and fretfulness, and increased vitamin-A concentration in the blood. The prognosis in recognized cases is excellent after cessation of excessive vitamin-A intake. Sulzberger and Lazar point out that exophthalmos occurred in an adult with hypervitaminosis A. This has previously been reported as occurring in experimental animals receiving large doses of vitamin A. In this adult, the hair of the eyebrows and lashes were lost.[304] Anaphylactic shock has been reported after intravenous administration of the vitamin B complex.[305]

Generalized Vitamin Therapy.—Pohlman and Ritter[306] notes a relation between vitamin deficiency and optic nerve disease, and Guha[307] reports beneficial results in a variety of ocular conditions with the use of vitamin A and B and ascorbic acid. Other authors[308] have discussed the merits of vitamin therapy in ophthalmology. Methods have been described for the detection of vitamin A by spectrophotometry.[309] Simkova has reported on the beneficial effect of thiamine hydrochloride and riboflavin on a variety of corneal diseases.[310]

Vitamin E has been shown to play a role in the metabolism of connective tissue and skeletal muscle. Massive doses of alpha-topherol, 1,200 mg., given daily did not prevent the gross development of keloids in the Negro. However, vitamin E will relieve the subjective discomfort of keloids, that is, the pain, burning, and tingling. The mechanism for this is not known; it may be based on capillary dilatation, and hence softening of the keloid.[311] A number of papers

300. Hanbold, H.; Lackner, F., and Schmidt-Lecker: New Therapeutic Experiences with Emulsified Vitamin A, Med. Klin. **46**:30, 1951.

301. Niedermeier, S.: Medicinal Effect on Night Vision, Deutsche med. Wchnsch. **76**:210, 1951.

302. Dekking, H. M.: Chemical Influence of Retinal Functions, Acta physiol. et pharmacol. neerl. **2**:141, 1951.

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304. Sulzberger, M. B., and Lazar, M. P.: Hypervitaminosis, A, J. A. M. A. **146**:788, 1951. Naz, J. F., and Edwards, W. M.: Hypervitaminosis A, New England J. Med. **246**:87, 1952. Gribetz, D.; Silverman, S. H., and Sobel, A. E.: Vitamin A Poisoning, Pediatrics **7**:372, 1951. Ojers, G. W., and Alfano, J.: Band Keratopathy in Disturbances of Calcium Metabolism, A. M. A. Arch. Ophth. **46**:531, 1951.

305. Chetwood, W. R., and Moore, C. D.: Anaphylactic Shock Following Intravenous Administration of Vitamin B Complex, J. A. M. A. **148**:461, 1952.

306. Pohlman, M. E., and Ritter, E. F., Jr.: Observations on Vitamin Deficiency, Am. J. Ophth. **35**:228, 1952.

307. Guha, G. S.: Role of Vitamins A, B and C in Affections of the Eye, Indian M. J. **45**:949, 1951.

308. Moren, A., and Pola, G.: Vitamin Therapy in Ophthalmology, Medicamenta **9**:395, 1951.

309. Bagnall, H. H., and Slock, F. G.: A Critical Account of the Spectrophotometric Estimation of Vitamin A, J. Pharm. & Pharmacol. **4**:81, 1952.

310. Simkova, M.: Influence of Local Treatment of Diseases of the Cornea with Vitamin B_1 and B_6, Československ. ofth. **7**:37, 1951.

311. Edgerton, M. T.; Hanahan, E. M., and Davis, W. B., Use of Vitamin E in Treatment of Keloids, Plast. & Reconstruct. Surg. **8**:224, 1951.

have pointed out the inadequacy of vitamin E in prevention of retrolental fibroplasia.[312] However, it has been shown experimentally that the lack of vitamin E alone caused degenerative changes in the retina and lens which were not influenced by additional doses of choline.[313] Stormont has demonstrated a seborrhea-like lesion developing about the eye and the corners of the mouth that may be due to the deficiency of pyridoxine, or vitamin B_6.[314]

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312. Laupus, W., and Bousquet, F.: Retrolental Fibroplasia, A. M. A. Am. J. Dis. Child. **81**:617, 1951. Dancis, J.; Lewis, J. M., and Guy, L. P.: Retrolental Fibroplasia: Statistical Study with Particular Reference to the Effect of Vitamin A, New England J. Med. **245**:402, 1951. Kramer, B.; Gordon, S. M.; Berger, H. M., and Sobel, A. E.: Aqueous Dispersions of Vitamins A and D in Premature Infants, A. M. A. Am. J. Dis. Child. **82**:17, 1951. Kinsey, V. E., and Crisholm, J. F.: Retrolental Fibroplasia: Evaluation of Several Changes of Dietary Supplements of Premature Infants with Respect to the Incidence of the Disease, Am. J. Ophth. **34**:1259, 1951.

313. Malatesta, C.: Histopathological Changes in the Eye in Experimental Avitaminosis E in Rats, Boll. ocul. **35**:31, 1951.

314. Stormont, R. T.: Pyridoxine Hydrochloride Vitamin B_6, J. A. M. A. **147**:322, 1951.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

James W. Smith, M.D., *Chairman*

A. G. DeVoe, M.D., *Secretary*

Regular Meeting, Jan. 21, 1952

The Physician's Opportunity in Preventive Ophthalmology. DR. ISADORE GIVNER.

Every physician has an opportunity to prevent blindness. The author discussed the peculiar problems related to ocular disease which may fall in the provinces of the internist, the anesthetist, the general surgeon, the dermatologist, the obstetrician, the pediatrician, and, finally, the ophthalmologist. In addition, he urged legislation to assure sterility of ophthalmic preparations and to insist that the pharmacist keep solutions sterile. He also urged that more thought be given to prophylactic eugenics as a means of preventing hereditary ophthalmic diseases.

DISCUSSION

DR. CONRAD BERENS: It is encouraging to all interested in the conservation of vision and the prevention of blindness to see this group showing an interest in this important work.

Although most physicians have daily opportunity to conserve vision in one way or another, their busy routine rarely permits them to give careful consideration to the way in which this may be accomplished. The thought-provoking paper by Dr. Givner is educational and highly constructive and will serve to stimulate interest in the prevention of blindness.

Glaucoma is the disease which accounts for 12 to 16% of blindness among adults in Canada and the United States, and is one in which early diagnosis and careful, continuous treatment will often prevent serious loss of vision. Early diagnosis of the chronic primary glaucoma is imperative, and more surveys (Carpenter, E. M.; Brav, S. S., and Seidel, V. I.: Experiment in Glaucoma Case Finding, *J. A. M. A.* **147:** 1127 [Nov. 17] 1951) like those made by the Philadelphia Society for the Prevention of Blindness are sorely needed. These authors examined 11,000 persons and found that between 2 and 2.5% had glaucoma and did not know it.

While it is important to make these surveys (and they should be encouraged), it is even more important to teach every general physician, every neurologist, and every neurosurgeon how to diagnose early glaucoma and give him an instrument with which he can make an early diagnosis of ocular hypertension.

Dr. Givner has referred to the hypertension indicator which was designed for the estimation of intraocular tension (Berens, C., and Tolman, C. P.: An Ocular Hypertension Indicator (Tonometer), *J. A. M. A.* **142:**1360 [April 29] 1950) and has asked me to say a word about it here. This instrument is essentially a small Schiøtz tonometer without the complicated indicating system, which, while it shows more gradations in tension, adds a mechanism that is unnecessary for the purpose of the average physician. The several additional parts greatly increase friction and augment the difficulty of keeping the tonometer in good working condition.

This simple tonometer is being used by the Ophthalmological Foundation as part of its program in educating physicians in measures to prevent blindness through a better understanding of the eye and its diseases.

No tonometer is distributed unless an ophthalmologist signs the application attesting to his willingness to instruct the physician in the use of the instrument. Lantern slides and phonograph records are available to the ophthalmologist in making these presentations.

Four hundred ophthalmologists were invited to cooperate. Of this trial group, 190 (47%) have accepted and are actively cooperating. These ophthalmologists are practicing in 90 cities, 33 states, and 14 foreign countries. In the talks given by ophthalmologists to physicians, they are encouraged to stress the broader aspects of the prevention of blindness from glaucoma and other systemic conditions of the eye.

An even greater field for the prevention of blindness from glaucoma is presented by the optometrists. It is estimated that the 22,000 optometrists in the United States see about 60% of the patients who believe they need glasses.

Ophthalmologists often state that optometrists should be more competent in recognizing ocular disease; yet no satisfactory scheme now exists whereby optometrists can recognize possible glaucoma, even though they write of plotting fields and are even giving consideration to flicker fusion fields (Wicks, Ralph S.: OD, A Report on Scleral Tonometry, *Optometric Weekly*, Nov. 1, 1951, p. 1720).

I have urged our National Committee on Interprofessional Relations to give consideration to this problem, and they will do so at the next meeting. This is an urgent and serious matter, which involves opticians as well as optometrists. Therefore, I hope that each state will soon have a Committee on Interprofessional Relations to consider this and other matters which are vital in the interest of the prevention of blindness and the public health. The Academy might well take the lead in this matter.

Dr. Givner is right in again warning the general practitioner, and, in fact, all physicians, concerning the danger of administering drugs which may lead to increased tension, and every physician should attempt to be certain that the newer, partially investigated preparations will not impair vision. We know that cataracts developed after the use of dinitrophenol, and later I also observed cataract as the result of using dinitrocresol, which was supposed to be free from the danger of producing cataract. I operated on four eyes and saw four others in which cataract resulted from use of these preparations, and these cases were not reported.

Although I agree with Dr. Givner that the ophthalmologist is not concerned with the treatment of diabetes, he can at least encourage and cooperate in research in cases of diabetic retinopathy (Berens, C., in discussion on Gifford, S. R.: Diabetic Retinopathy), Symposium on Diabetic Retinitis, *Am. J. Digest. Dis.* **10:** 329 [Sept.] 1943). Certainly, the field of chronic infection should receive careful study, as was pointed out several years ago. The warning to surgeons concerning malignant exophthalmos is timely. Furthermore, neurologists and neurosurgeons should be cautioned to seek ophthalmologic consultation before making the diagnosis of papilledema. Having seen total disinsertion of the upper half of the retina in the only seeing eye of a patient with atopic dermatitis, I feel certain that the warning to dermatologists in cases of this serious skin lesion is completely warranted. We should stimulate the interest of obstetricians in research in the prevention of maternal illness in the early months of pregnancy. We should cooperate with pediatricians and other scientists in the hope of lessening the blindness which results from these congenital anomalies, which we hope some day will be preventable.

It is important to continue to stress the need for properly administered prophylaxis against ophthalmia neonatorum, even though the incidence of blindness

from this disease has been greatly reduced (Berens, C.: Ophthalmia Neonatorum, *Am. J. Obst. & Gynec.* **47:** 855 [June] 1944).

Any change from the use of silver nitrate for the prevention of ophthalmia neonatorum is premature until we have more well-controlled studies (Berens, C., and Foote, F. M.: Penicillin or Silver Nitrate as a Prophylactic Against Ophthalmia Neonatorum?, *Am. J. Pub. Health* **38:** 12 [Dec.] 1948).

It is impossible to believe that pediatricians still advise parents to permit their children to "outgrow squint," but I have seen three children in the past year who have been so advised. This is one more instance of need for education of physicians by ophthalmologists. Because of association with the program on industrial ophthalmology sponsored by Columbia and New York Universities, it has become apparent to me that we must stimulate more ophthalmologists to enter the field of industrial ophthalmology and must continue to teach industrial physicians. This can best be accomplished through university participation in these programs on a much broader scale, and ophthalmologists must help to organize these activities.

I suggest as an addition to the wise rules for surgery which have been outlined, and which include ruling out infection in the lacrimal sac, that all chronic infections be carefully investigated prior to operation; furthermore, that every effort be made to eliminate these infections prior to surgery or that control be attempted with antibiotics and the effort made to raise general and local resistance to infection. The point about the preoperative use of penicillin is well taken.

We certainly should do everything possible to prevent infection from our tonometers. Although a new sterilizing stand has been constructed for the Schiøtz tonometer, I am still debating the best solution to use for sterilization. I used alcohol for years, but some time ago I turned to ether because of the gumming of the plunger which resulted from alcohol. Aqueous benzalkonium (zephirans®) chloride caused severe irritation in several cases. I hope Dr. Givner will tell us what to use.

His suggestions for keeping ophthalmic solutions sterile, for inhibiting Pseudomonas aeruginosa, and for legislation to insure sterility of pharmacists' prescriptions and those of the manufacturing chemists are most constructive and important.

We should be particularly grateful for this scholarly discussion of hereditary and congenital diseases of the eye and their prevention. It might be well for the Academy to appoint a committee to investigate the subject of hereditary ocular disease. This committee might want to explore with both ophthalmologists and geneticists the possibility of setting up a central file with complete records of affected families, and might work with social and religious agencies on recommendations for methods of control.

The essential need is for more research into causes of prenatal blindness. Statistical studies indicate that blindness from known causes is being reduced, but cases of blindness of unknown cause are increasing (Kerby, C. E.: Trends in Causes of Blindness in New York State, *Sight-Saving Rev.* **21:** 215 [Winter] 1951). According to 1949-1950 figures, 15.6% of blindness in the United States is hereditary and 48.5% is of prenatal origin, with the cause not specified.

It is of vital importance to encourage the development of an organization for the prevention of blindness in every state in the Union, and this is something every ophthalmologist can help to accomplish.

DR. RALPH I. LLOYD, Brooklyn: The ophthalmologist is favored by the opportunity of acquiring objective evidence in his cases. This tends, to a certain extent, to his undervaluating other methods of examination; as a result, perimetry is one of the procedures he is apt to neglect. This tendency to admit nothing but an absolute certainty by using only objective evidence narrows the physician's point of view, and specialists are apt to limit their examination and observation to the organ in which they are interested. As a result, it is not unusual in cases of sudden

blindness in one eye for the ophthalmologist to miss the benefit to be obtained by examining carefully the second eye by every method at his disposal. Also, patients come into the office complaining of their eyes who bear the physical evidence of the basic cause. I have two slides to illustrate what I am trying to say. I am sure that most of you will expect me to introduce a case of arachnodactyly to prove the point, but I am going to fool you by showing a case of cranial dystrophy in a patient who appeared because of the divergence of the right eye. (Slide). Here is evidence of what is called hypertelorism, with the inevitable strabismus divergens and the typical craniofacial deformity, with the short upper lip, the unusual breadth between the eyes, and the flattening of the skull from above down.

The second slide shows the field chart of a patient who complained of sudden loss of sight in the right eye occurring overnight. It may not have happened as suddenly as that, but that was his story. Neither fundus showed anything abnormal. The patient was then referred to a rhinologist, who reported chronic ethmoiditis, for which operation was performed. The tissue removed was sent to a pathologist, who made the diagnoses hypertrophic rhinitis; this was considered adequate cause for the loss of vision. Thereafter the patient went to another man, who examined the apparently well eye and found loss of the superior temporal quadrant and part of the lower temporal quadrant. In a short time the remaining temporal sector of this eye was lost. The temporal hemianopsia in one eye with blindness in the other immediately gives a clue to the location of the lesion. Up to this time vision was 20/20 in the functioning eye. After a while vision of the right nasal sector was lost, as well as the knee jerks, and the other symptoms of tabes dorsalis appeared.

At the present day the average oculist, whether in his private office or at a hospital, has many aids, and these people have felt the economic pressure more than most. As a result, their minds are turned toward the question, to them the most important, of security, and they are keenly alert to the eight-hour day and to as much pay as they can get, for which one cannot blame them. But the effect of this divergence of attention of the lower section of our hospital help, particularly in city hospitals, is very evident in the service they give. In his office, the physician is personally responsible for his helpers, and in the hospital he may not be legally responsible, but he is morally responsible. This is a load acquired slowly, but surely, and it will no doubt grow as time goes on. Most of the lapses are no more than annoyances, but some are indeed serious and result from faulty preparation and handling of drops in common use everywhere.

There is a source to which we should always turn for help as to what is going on in general medicine. By that I mean that every ophthalmologist should have at least one of the large successful journals in general medicine, like *The Journal of the American Medical Association*. In that he can keep track of what is going on, and various events of great value in his practice will be called to his attention. I shall cite one instance. Some years ago a depilatory ointment was sold in department stores, $10 for 2 oz. As a result of its use, a number of cases of optic atrophy of very severe type developed; in this community we were at a loss as to the cause, until someone sent a specimen of the ointment to the Laboratory of the Council on Pharmacy and Chemistry of the American Medical Association. They demonstrated that this ointment was a thorium preparation in a fatty medium and that it produced symptoms not unlike lead poisoning. All of us want our specialty to maintain the high position it holds; we do not want anyone to say of us that we are specialists of the type who know more and more about less and less. The public is well aware that medical service is always available for those who do not pay, as well as for those who do, and this is the reason that "socialized medicine," of the type in vogue in England, has not prevailed here. Ophthalmology must continue its efforts to hold closely with the rest of the medical profession to the professional ideal—that the welfare of the patient is at all times paramount.

DR. FREDERICK H. THEODORE: I have time to mention only two points. The first concerns the sterility of ophthalmic solutions. After the letter which Dr. Minsky and I published, *J. A. M. A.* **147:** 1381 [Dec. 1] 1951), and also perhaps as a result of my editorial (*Am. J. Ophth.* **34:**1764 [Dec.] 1951), the Council on Pharmacy and Chemistry of the American Medical Association has now voted that all ophthalmic medicaments should be sterile. They have also written me that it may not be necessary to pass a national law to this effect, because if the Pharmacopeia and the National Formulary will include this requirement in their publications, the Food and Drug Administration can then demand that all ophthalmic solutions be, accordingly, sterile. I am happy to state that when I presented the facts to the Council they acted with great expedition.

My second point concerns Pseudomonas aeruginosa (Bacillus pyocyaneus). I agree entirely with Dr. Givner that sodium propionate is not bactericidal against this organism. No one has ever claimed this. It is, however, bacteriostatic. One must not confuse the two actions. Had Domagk depended only on bactericidal tests, he would have been discouraged and would never have introduced sulfanilamide into therapeutics. Generally speaking, none of the sulfonamides, nor any of the antibiotics, except penicillin in a high concentration, is bactericidal. If we considered only bactericidal tests, we would lose all the new advances we have made in these past years with the newer anti-infective agents. Dr. Givner tested one strain from an infected bottle of cortisone. Dr. Theodore Anderson, associate professor of bacteriology at Temple University, has tested over 50 strains of Pseudomonas, including a strain I sent him that was obtained from a similarly infected bottle of cortisone, as a matter of fact, from the same batch as Dr. Givner's. Dr. Anderson reports that in every strain he tested, using a 5% solution of sodium propionate at pH 7.0, he obtained inhibition zones measuring from 20 to 40 mm. in diameter. He agreed that sodium propionate is bacteriostatic, and not bactericidal. It should be stressed, however, that the best drugs in the treatment of Pseudomonas infections appear to be polymyxin, streptomycin, and neomycin. In my own experience, I have used a combination of streptomycin and sodium propionate with excellent results in cases of severe pyocyaneous ulcer of the cornea.

Concerning benzalkonium (zephiran®), one must stress that the drug has proved disappointing when carefully tested. Dr. Givner's results are unusually good. It should be pointed out that "New and Nonofficial Remedies" (1951) states (page 82) that certain strains of Pseudomonas aeruginosa are particularly resistant to the quaternary ammonium compounds, such as benzalkonium. One must be cautious about the use of benzalkonium in other ways. In preparing the operative field, it is ineffective to use soap and not remove it thoroughly. Many hospitals have returned to the use of iodine, rather than trust an aqueous benzalkonium solution.

DR. ISADORE GIVNER: As to what I use to sterilize tonometers, I still use a very weak benzalkonium solution (1:20,000), and it seems to be satisfactory.

In regard to Dr. Theodore's statement, there are various strains of Pseudomonas. Some years ago I wanted to do experimental work on pyocyaneus ulcer of the cornea. I had several cultures but could not produce an ulcer when I wanted to; so it is evident that the various strains differ in their pathogenicity. In the present work we used only one strain, that recovered from an ulcer of the cornea, and with this strain benzalkonium seemed to be effective. It is true that with another strain the drug might not work as well as other agents.

Use of Corticotropin and Cortisone in Ophthalmology. DR. ALAN C. WOODS, Baltimore.

The author emphasized the use and limitations of these drugs, noting that their value is limited to the combating of inflammation and exudation. Chronic ocular

diseases recur almost immediately after cessation of use of the drug. It is important to combine corticotropin and cortisone with adequate chemotherapy. Although in nongranulomatous uveitis results are spectacular, effects are not so striking in granulomatous uveitis, in which there is actual bacterial invasion. In central serous retinitis results are always good. In optic neuritis results are less good, but the drugs are probably indicated. In diabetic retinopathy, Eales's disease, retinitis pigmentosa, arteriosclerosis, and the exophthalmos of toxic diffuse goiter the drugs have failed. About 50% of cloudy corneal grafts have been improved by topical application of cortisone. At present the results in retrolental fibroplasia have not justified the use of these drugs. The author pointed out that keratoconus, Mooren's ulcer (rodent ulcer of cornea), and marginal dystrophies may be collagen diseases.

The usual doses of corticotropin employed are 120 to 160 mg. the first day, the amount being dropped gradually in accordance with the therapeutic response to 30 to 40 mg. per day. The dose of cortisone is usually 300 mg. the first day; it is then dropped to 200 mg., and then decreased 100 mg. daily, being finally tapered off to 40 to 50 mg. a day. The topical use of cortisone is as effective as the parenteral use in infections of the anterior segment, the author preferring application in ointment form every three hours. The intravenous administration of corticotropin in glucose drip over an eight-hour period has 8 to 12 times the effect of the same amount given intramuscularly. It was noted that the chief effect of the drugs is at the cell level, with the suppression of the inflammatory phase. It has no effect upon the underlying sensitivity mechanism. Epithelial regeneration is not impaired, but the stromal response is greatly decreased when the drugs are given in large doses (30 times the therapeutic level). There is no practical effect upon the healing of ocular surgical wounds when the doses are held in the usual therapeutic range.

DISCUSSION

DR. LUDWIG VON SALLMANN: As to the evaluation of clinical results obtained in the treatment of ophthalmic diseases with cortisone and corticotropin, there is fair agreement among investigators who have had the opportunity to accumulate extensive data, and also have the clinical experience to distinguish between therapeutic effects and the spontaneous variations in the course of the disease. Blocking of symptomatic manifestations of an inflammatory reaction and therapeutic suppression of tissue reactivity by the hormonal agent have been seen by all investigators in the past one or two years, in complete accord with the original, early observations of Dr. Woods and of Dr. John McLean and associates. Deviations from these findings, may be explained in part by the differences in the doses employed or by differences in the treatment schedule and method of administration, as implied by Dr. Woods, or as shown by Schulman's remarkable results in Boeck's sarcoid with the intravenous use of corticotropin. That brings me to my first question: Does the occurrence of protein shock in connection with the intravenous use of corticotropin constitute a real danger, or is it too rare to influence the indication for this type of administration?

Negative results or failures of treatment with the hormonal drugs under discussion may result not only from inadequate dosage, but, as indicated on one of the slides shown by Dr. Woods, from persistence and severity of the inflammation produced by a toxic agent. This relationship was strongly suggested in unpublished experiments of the Knapp Memorial Laboratory on animals in which a graded type of endophthalmitis was produced by intraocular injections of variously diluted solutions of purified staphylotoxin. In contrast to the beneficial effect of cortisone therapy observed in mild inflammation, severe endophthalmitis was not influenced by local or systemic use of cortisone, either in its clinical symptoms or in the qualities of the cytograms obtained from the withdrawn and centrifuged aqueous humor.

Dr. Woods contributed greatly to the understanding of hormonal therapy in tuberculous infections of the eye, confirming the general impression that this type of treatment harbors great danger. It would be of great profit to us all if he would give us the benefit of his opinion in a related question of great practical importance, that is the advisability of the use of cortisone and corticotropin in addition to adequate chemotherapy of ocular infections. A priori, it seems advantageous to interpose a block between the toxin resulting from a bacterial invader and the peripheral tissue cells. However, unfavorable effects of cortisone therapy have been reported in animal experiments, not only in infections with Mycobacterium tuberculosis, which Dr. Woods has discussed so elaborately for us, or in infections with Treponema pallidum, mentioned in the discussion of the treatment of interstitial keratitis, but also in animal infections with staphylococci, streptococci, Brucella and viruses. Is it fair then to assume that the use of cortisone and corticotropin in combination with antibiotics reduces the benefits derived from the specific antimicrobial agent, or should this general impression be modified with respect to infections of the eye, whose characteristics differ from other infections of the body?

In view of the meager knowledge we have of the mechanism of the action of cortisone and corticotropin, many questions could be asked of Dr. Woods, and we would certainly learn from his answers. I shall limit myself to a question concerning his statement on the effect of cortisone on capillary permeability in the normal and the inflamed eye. Experiments were carried out by two groups in the research department of the Institute of Ophthalmology, and two different conclusions were reached. One group found a slight decrease in permeability of the ciliary capillaries in the normal eye with the animal under systemic cortisone treatment, while Sullivan noted an increase in the permeability of these capillaries to protein and fluorescein. This increase was also measurable when the eyes were under the influence of diisopropyl fluorophosphate. Moreover, studies by Fritz, in Belgium, and other investigators gave different results, proving that it is not yet known what cortisone and corticotropin do to the capillaries of the eye in normal and pathologic conditions.

Dr. Alan C. Woods: Dr. von Sallmann has asked three questions. The first question is: Is the protein reaction which may possibly be seen with intravenous corticotropin treatment a contraindication to such use? I have never had any trouble with it as we have used it, and I do not think I should list the reaction as one greatly to be feared. I should be more concerned about its effect on the glomeruli of the kidneys, because we have seen that cortisone- and compound-F-treated rabbits frequently showed Kimmelstiel-Wilson capillary aneurysms in the glomeruli. There have also been several cases—a notable case being that of a man treated intensively with corticotropin for an ocular condition who later died of generalized carcinomatosis, and whose kidneys showed these capillary aneurysms in the glomeruli.

Dr. von Sallmann's second question is: In bacterial infection, is not the imposition of a barrier between the cell and the toxin beneficial? How much danger is there in masking symptoms? There was a famous case in Boston in which a man with pneumonitis was treated with corticotropin. He made a symptomatic recovery from his pneumonitis, but his blood culture showed myriad colonies on every blood plate; he was loaded down with pneumococci. It is, on the other hand, quite possible that by the use of proper auxiliary therapeutic measures we may be able to avail ourselves of the benefit of a block between toxin and cell. I hope that in the course of the next three or four months I can answer that question. My colleagues and I are now running a large group of rabbits with ocular brucellosis, these rabbits being treated with corticotropin, cortisone and compound F. Within two or three months we should know whether the rebound phenomenon occurs in these rabbits which we observed in tuberculosis. In other words, will hormone therapy have the same effect as in tuberculous lesions? If it has, the next step would

be to inject rabbit eyes with tubercle bacilli and treat them with streptomycin and paraaminosalicylic acid in conjunction with hormonal therapy. Thus, it might be possible to kill off the organisms while they are unphagocytosed and not encapsulated. If hormonal therapy has the same effect on the Brucella infections as it did in tuberculosis, a similar series of rabbits should be treated with aureomycin plus hormonal therapy. All these questions can be answered by experimental observation, but I cannot do so now.

The third, and last, question was about capillary permeability; I know nothing about it except what I told you. I have never worked on it myself. I have given you the results of others' experiments—some done in the Wilmer Institute and some in London. The consensus of the published reports is that these drugs have no effect on the capillary permeability of the normal eye; and then there is Ashton and Cook's remarkable observation that they affect the increased capillary permeability due to inflammation.

As to the reaction to stimuli, we have had results similar to those outlined by Dr. von Sallmann. One can see this especially well with jequirity infusions; a strong suspension will cause a necrotic lesion and rupture of the eye in two or three days, while a weak suspension (1:128,000) will give only a weak reaction. The weak reactions we can suppress; the strong reactions we cannot. Likewise, the dose of the hormone is important; we can inject 2.5, 5, or 10 mg. of cortisone in the anterior chamber and get a suppression related to the size of the dose. With the large dose there is complete suppression; with the smaller amounts, only partial suppression, and with still smaller amounts, none. It is a relative reaction, and definitely a quantitative one.

News and Comment

GENERAL NEWS

1952 New York Clinical Congress, American College of Surgeons.—The programs for the Section on Ophthalmology are as follows:

Sept. 23, 1952: 9:00 to 10:30 a. m.: Panel discussion on Problems Concerned with Extraction of Complicated Cataracts

Moderator: John H. Dunnington, M.D., F.A.C.S., New York
Collaborators: Walter S. Atkinson, M.D., F.A.C.S., Watertown, N. Y.;
Henry L. Birge, M.D., F.A.C.S., Hartford, Conn.;
Glen Gregory Gibson, M.D., Philadelphia

8:30 p.m.: Symposium on Surgical Correction of Motor Anomalies Involving the Extraocular Muscles

Surgical Physiology of Extraocular Muscles	Harold W. Brown, M.D., New York
Surgical Correction of Esotropia	
Surgical Correction of Exotropia	Harold G. Scheie, M.D., F.A.C.S., Philadelphia
Surgical Correction of Vertical Muscle Anomalies	Walter H. Fink, M.D., F.A.C.S., Minneapolis
Surgical Correction of Blepharoptosis	Raynold N. Berke, M.D., Hackensack, N. J.

Sept. 24, 1952: 9:00 to 10:30 a. m.: Panel discussion on Orbital Implants

Moderator: Arno E. Town, M.D., F.A.C.S., New York
Collaborators: Alston Callahan, M.D., F.A.C.S., Birmingham, Ala.
John P. Macnie, M.D., F.A.C.S., New York
Raymond E. Meek, M.D., F.A.C.S., New York

8:30 p. m.: Symposium on Causes of Failure in Ocular Surgical Procedures

Pathological Causes of Failure Following Intraocular Operations	Brittain Ford Payne, M.D., F.A.C.S., New York
Failure in Glaucoma Operations	Joseph A. C. Wadsworth, M.D., New York
Failure in Cataract Operations	Daniel B. Kirby, M.D., F.A.C.S., New York
Failure in Extraocular Muscle Surgery	Truman L. Boyes, M.D., F.A.C.S., New York
Failure in Retinal Detachment Surgery	P. Robb McDonald, M.D., F.A.C.S., Philadelphia

Sept. 25, 1952: 9:00 to 10:30 a. m.: Panel discussion on Fallacies in Refraction by Use of Mechanical Refractors

Moderator: Conrad Berens, M.D., F.A.C.S., New York
Collaborators: Alfred Cowan, M.D., Philadelphia
Arthur Linksz, M.D., F.A.C.S., New York
Daniel Snydacker, M.D., Chicago

8:30 p. m.:

Sympathetic Ophthalmia
Harold H. Joy, M.D., F.A.C.S., Syracuse, N. Y.
Discusser: George M. Haik, M.D., F.A.C.S., New Orleans

Atomic Eye Injuries
Brig. Gen. Elbert DeCoursey, M.C., U.S.A.
Discusser: David G. Cogan, M.D., Boston

Management of Intraocular Foreign Bodies
Raymond L. Pfeiffer, M.D., F.A.C.S., New York
Discusser: Norman L. Cutler, M.D., Wilmington, Del.

Treatment of Eye Burns
Robison D. Harley, M.D., F.A.C.S., Atlantic City, N. J.
Discusser: Hedwig S. Kuhn, M.D., Hammond, Ind.

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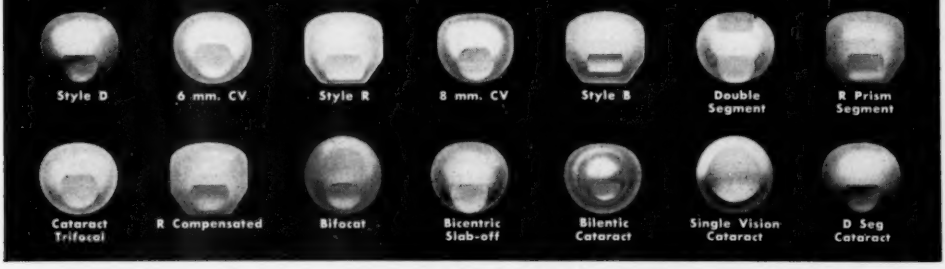

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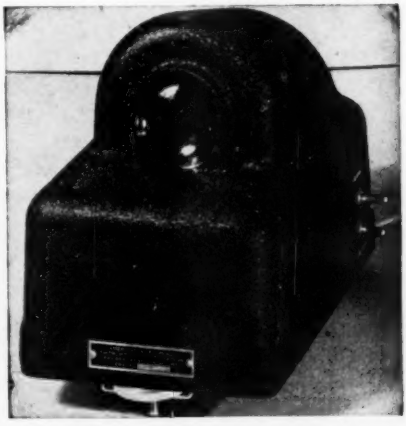

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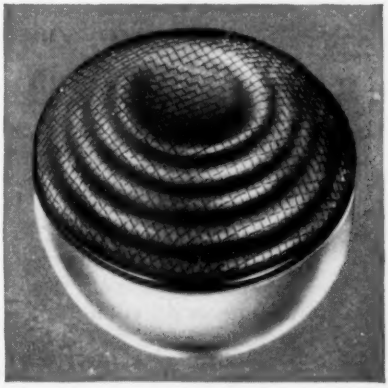

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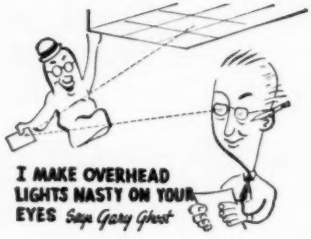

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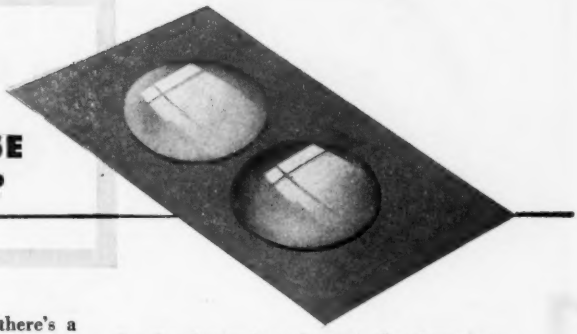

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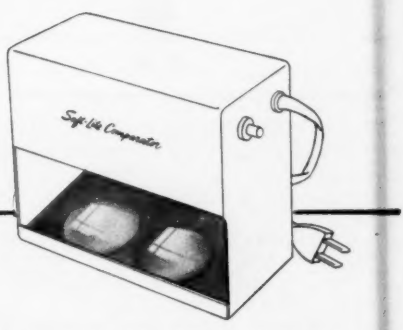

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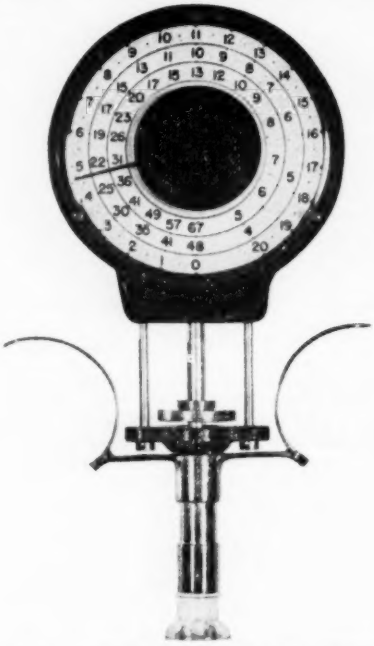

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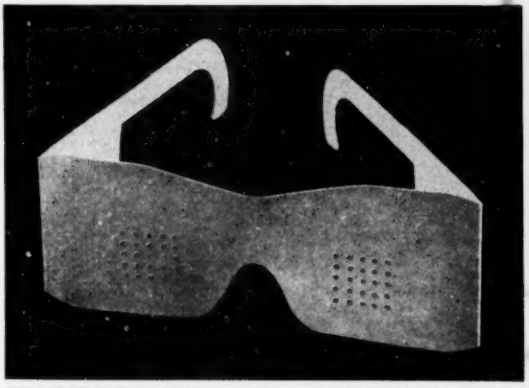

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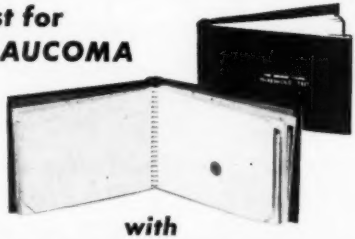

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1. Scheie, H. G., Tyner, G. S., Buesseler, J. A., and Alfano, J. E., *J. A. M. A. Arch. Ophth.* 45:301, March 1951.

2. Leopold, I. H., Purnell, J. E., Cannon, E. J., Steinmetz, C. G., and McDonald, P. R., *Am. J. Ophth.* 34:361, March 1951.

Literature on request

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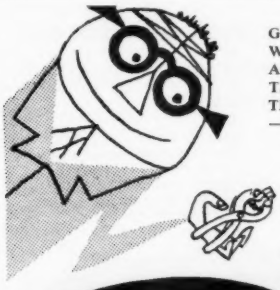

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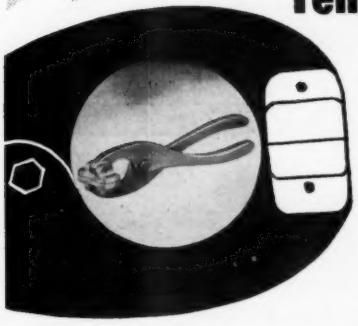

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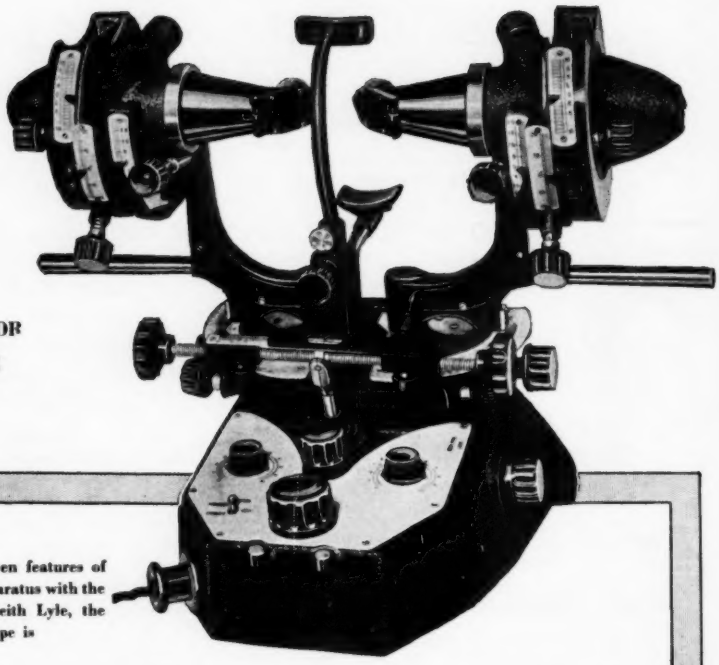

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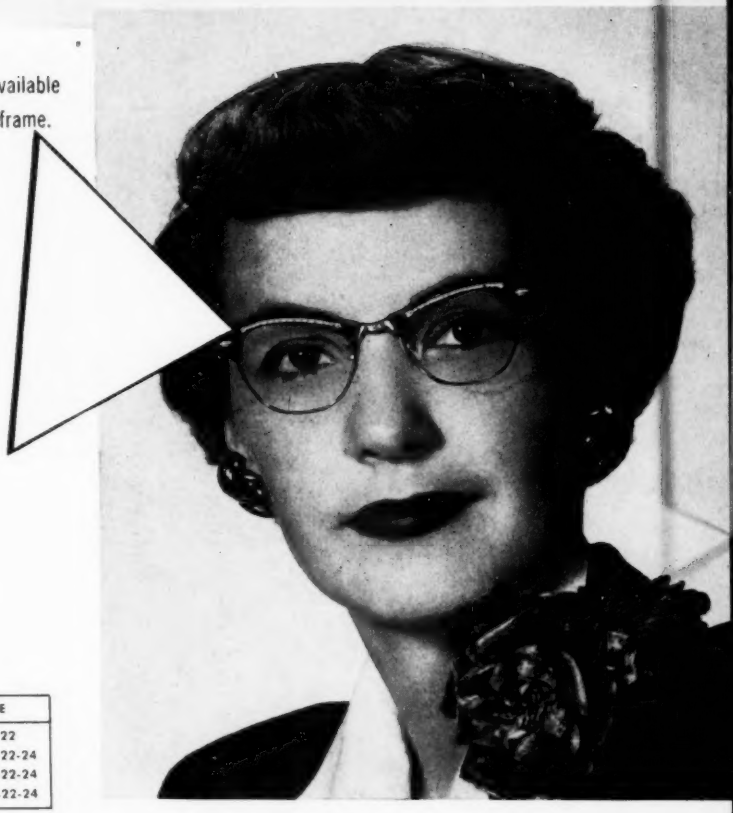

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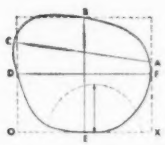

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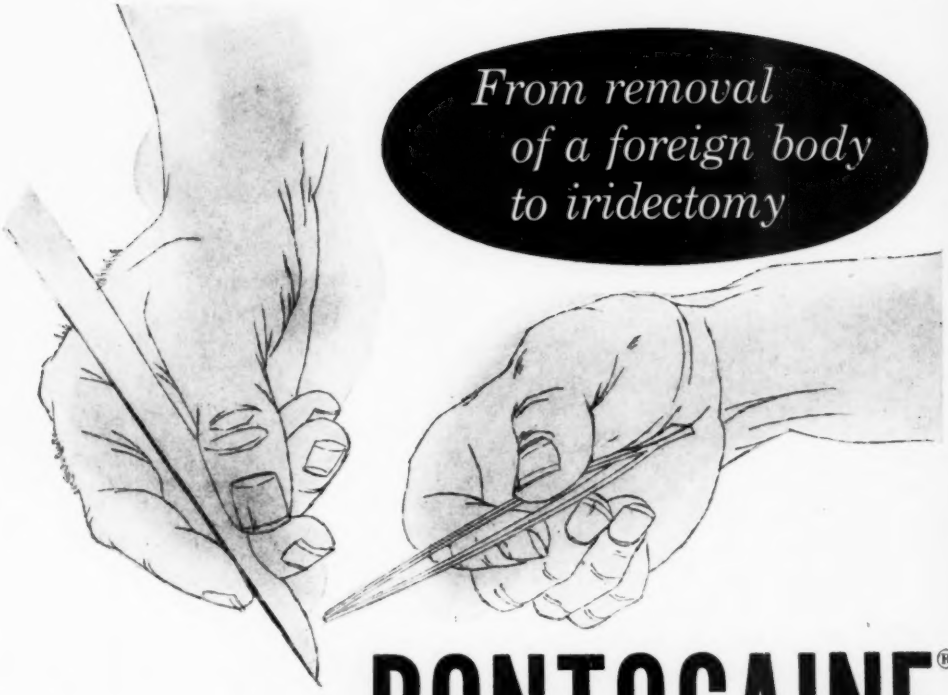

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